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Section of Anæsthetics

President—H. P. FAIRLIE, M.D.

[*December* 1, 1933]

Intrathecal Nerve Root Block. Some Contributions and a New Technique[1]

By W. ETHERINGTON-WILSON, F.R.C.S.

To become expert in the art of spinal analgesia is no simple matter for the beginner, for many solutions and techniques are available and many problems present themselves which form subjects for discussion and disagreement. The literature is abundant, very illuminating and worthy of a very close inspection for a beginning. One essential aspect of the subject, however, is deplorably lacking, e.g., experimental work carried out with fluids of known densities in imitative spinal canals of glass, a study I have termed " mock spinal analgesia."

However closely the whole subject of spinal block is considered and followed by a fair experience of a number of cases, there still remains in many minds a vague fear, an uncertainty, a lack of confidence. Failures, partial or complete—uncontrollable results—unexplained effects—help to produce this inferiority complex. The remedy, surely, is a more perfect understanding of the behaviour of the injected solution in the subarachnoid space.

Mock spinal block experiments definitely make such necessary visualization possible and the importance of this method of study cannot be exaggerated. After carrying out hundreds of experiments during the course of nine months, I soon discarded the obvious criticism that an inert glass canal must give worthless results, when compared with the more active human spinal canal. From these mock experiments much is learnt, visualization becomes possible and confidence replaces fear and uncertainty.

Apparatus.—Figs. A and B show the type of apparatus used in these experiments. The illustrations show glass canals of different calibres and curves, mounted on boards with markings indicating certain anatomical levels, straight tubes for simultaneous injection and comparison experiments, a tiltometer for measuring angles, syringes, artificial spinal cords and a seconds-hand clock for estimating the time taken by the injected fluid to produce results under varying conditions. Various solutions are shown and these are usually dyed; eosin, methylene blue, indian ink, etc., make excellent stains. The coloured injection and the mock cerebrospinal fluids are sugar and salt solutions made to the required density: thus the cerebrospinal fluid is taken at specific gravity 1·007, percaine 1·003, etc. It is quite unnecessary to use actual solutions, for they behave in the same way as the home-made. It is only essential to see that the mock injection and the cerebrospinal fluid are of the correct density, and they should be at the same temperature when prepared.

Types of experiments.—The number and variety of experiments which can be carried out seem almost endless; many are of little practical importance; all sharpen the visual picture and assist in the acquirement of a knack. We learn about methods of mixing, rates of ascent and descent of solutions and the factors which may

[1] This paper was illustrated by a two-reel cinematograph film.

influence them, e.g., angles of inclination, curves of column, solid structures within the canal, pulsation, temperature, varying the density of the fluids, varying the amount of injection, the effect of different methods of injecting the solution, the behaviour of alcoholic solutions. A few of the more important of these results were incorporated in a cinematograph film.

A definition.—The ideal requirements of perfect intrathecal nerve rootlet block may be stated in the following way. The introduction of an analgesial solution in minimum dilution and dosage into the subarachnoid space. The drug should be non-toxic, so that after absorption (which takes place rapidly) into the circulation it may not interfere with the general processes of metabolism or hinder the proper functioning of the bulbar centres. The dose decided on must be delivered as a whole into the cerebrospinal fluid. It is not recognized sufficiently that it is easier to

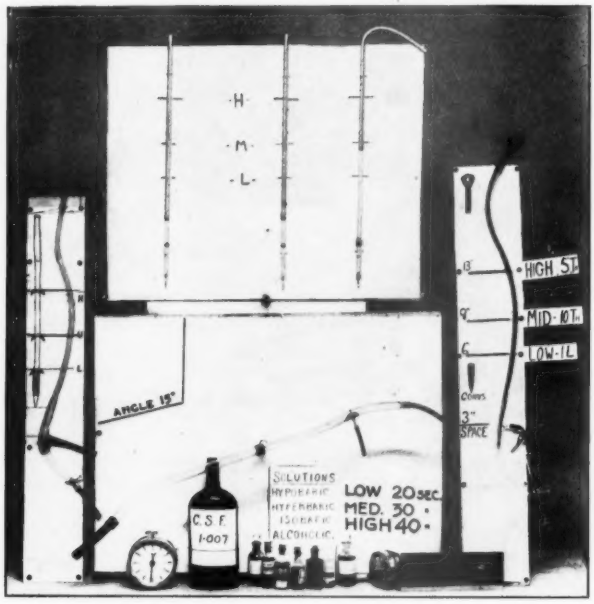


FIG. A.

draw off cerebrospinal fluid than to insert something into it, along the same needle. The fouling of the needle eye by the dura and possibly the arachnoid are responsible for this error, the result being that part of the whole of the solution may be deposited extradurally. The remedy is simple. To ensure complete delivery the needle eye must pass further into the canal and get clear of the rather easily mobilized, posterior, dural lining. The distinct danger of injuring the cord is overcome by using an interspace which is never in relation to this structure. The 3rd lumbar intervertebral space is undoubtably the highest safe space in the adult. It is probable that a blunted needle may at times push a cone-like process of dura forwards before penetration, which suggests another reason for using a safe interspace.

The solution introduced must be capable of travelling and should move upwards, to avoid waste in the sacral canal, in order that the spinal cord and rootlets shall

be bathed. Manifestly the latter fibres will be more easily affected than the more coarse roots themselves and particularly the anterior motor roots. The solution having reached a required nerve segment which forms the upper boundary of the operation zone, it should be stopped from ascending further and producing higher and unnecessary segmental blocks. In short, we should be able to produce an

FIG. B

accurate area of analgesia sufficient for the operative needs, and thereby dosage is able to be kept at a minimum. In order to get a complete result, e.g., an anterior and posterior rootlet block, the solution must mix well with the cerebrospinal fluid so that it may be brought in contact with all nerve tissues in this area equally. The analgesia must outlast the surgeon's time of operating comfortably; there

should be no need for hurry, or supplements. Having set out to produce spinal analgesia let it be a spinal and there should be no need for further toxic adjuncts.

Consider intrathecal block in three main zones: (1) A low zone, bounded above by the 1st lumbar nerve segments (Poupart's ligaments), for operations on the lower limbs and perinæum. (2) A medium zone, bounded above the 10th thoracic segments (umbilicus), for operations on the lower abdomen and pelvis. (3) A high zone, bounded above by the 5th thoracic segments (nipple area), for operations on the upper abdomen and lower thorax.

Intermediary zones should also be obtainable, as in cases of par-umbilical hernia, inguinal hernia, and operation on the foot. Here we require a high median, a high low and a low low analgesia. The lower the block, the smaller the dose, the less effect on the patient. The technique should be considered safe, simple to understand, controllable and sure in action. The immediate and remote after results of all kinds should compare very favourably with other forms of anæsthesia, so that the many who still avoid this form of anæsthetic may be induced to recognize its value. The percentage of failures, which will always be in direct proportion to the skill and knowledge of the anæsthetist, can be reduced to a minimum, and should be capable of explanation and correction.

A patient should not be given a spinal anæsthetic when in complete possession of his senses. Sleepiness, amnesia, and loss of fear—in some degree—are easily produced by hypnotics. The nervous patient is not barred from spinal analgesia. The induction should not be in any way unpleasant; lumbar puncture can be done painlessly.

In order to attempt to conform to the ideal requirements stated above we must acquire a knowledge of the subject generally, a study of anatomy in relation to many side issues, and a knowledge of mock spinal analgesia in glass canals and in the recent dead body. There must exist a clear and fixed idea that most failures and probably the majority of complications are due directly to carelessness and errors in technique and are therefore avoidable.

Anatomical.—The technique to be mentioned consists, briefly, in allowing a light solution (percaine) to ascend up the vertical spinal canal and timing it to reach certain levels. The run being a straight one from the 3rd lumbar space to the 4th dorsal vertebra (5th thoracic nerve rootlets), we are not concerned with the curves of the spinal canal to any extent. The lumbosacral and cervicodorsal forward convexities are fixtures, in comparison to the intervening adjustable dorsilumbar column. The canal tends to be divided into compartments by the spinal cord, anterior and posterior roots, dentate ligaments and posterior median septum. Theoretically, it would appear best to inject a solution below the conus medullaris and allow it to ascend vertically so that the hypobaric fluid may enter these divisions and ascend along them. Solid structures, like the contents of the spinal canal, allow a solution to ascend but they have a brake action on its rate of travel. Yet it so happens that the rate of ascent of percaine up a spinal glass canal with no solid contents is approximately the same as in the actual human canal. The reason for this is that the glass canal also produces a brake action on the ascent rate of percaine, because the same cubic space is occupied by a larger quantity of cerebro-spinal fluid. As it mixes with the injected lighter solution, it is making it heavier and the higher the solution travels the slower the rate of ascent. Ascent rates are very similar in glass and human spinal canals.

Examination of a number of spinal canals, spinal cords, and skeletons (Royal College of Surgeons Museum) of various heights, enables certain distances to be measured. It is not proposed to mention a complicated number of figures. The distances required are those from the needle in the 3rd lumbar space to the 1st lumbar, 10th thoracic and 5th thoracic spinal nerve rootlets. It is sufficient to know whether the adult is short (5 ft. or slightly less), average height (5 ft. 8 in. to

10 in.) or tall (6 ft. 2 in.). The average distances are 6, 9 and 13 inches and one inch taken away or added on supplies the figures for the other two types of stature. The figures 6, 9 and 13 inches will be used throughout as representing the space to be traversed by an ascending fluid to produce low, median or high areas of block (see fig. B p. 11).

The dura is not attached firmly to the posterior wall and lies on a variable layer of extradural fat. It has been mentioned that a blunt needle may at times raise it from its bed. In looking at anatomical specimens it is almost impossible to imagine that any quantity of cerebrospinal fluid can leak after a puncture. Dense structures must prevent a leak outside the bony canal. Seepage into extradural fat does not seem likely because (1) it is improbable that a clean puncture in the dura remains patent; (2) it pre-supposes that the arachnoid puncture also remains open and opposite the dural stab; (3) extradural fatty tissue is more likely to act as a cork, when the dura is pressed back against it by the pressure of the subarachnoid fluid; (4) there is a type of headache which *develops a few days after* an operation, made worse by moving about and sitting up and relieved rapidly by lying flat or in the head down position: this phenomenon cannot be due to leakage; (5) in the operation of laminectomy a very great deal of cerebrospinal fluid is lost, yet headache is not a great feature of all these cases.

Physical.—Absorption of the injected solution which takes place very rapidly in the human canal is the great absent feature in mock experiments and has to be taken into account, otherwise it would be very tempting to believe from experiments that an ascending solution must reach the cervical and cranial subarachnoid spaces even after the safe interval has elapsed. The best proof of rapid absorption lies in the fact that after a few minutes a level of analgesia is established which cannot be altered to a higher area of block by appropriate sloping of the canal.

If absorption is rapid, the patient must get a large dose of the drug into the circulation rather suddenly and this seems a possible source for many headache cases and temporary palsies of nerves, particularly the intracranial. These no doubt arise from a cerebral œdema. Cushing has suggested œdema as a cause in the case of the abducent nerve, which becomes strangulated for a time by the strap-like action of the anterior inferior cerebellar and internal auditory branches of the basilar artery, which cross its course at right angles on the ventral surface of the pons. Œdema within the cranium we know does not clear rapidly and in this respect differs from œdema elsewhere. It is not surprising therefore that many after-effects should be met within the skull. The common occipital headache, fleeting or otherwise, may be connected with the fact that in this area, the meeting place of many venous sinuses, there is a large dose of the drug present, and venitis or a meningeal irritation may conceivably result. From glass canal experimental evidence, it does not seem possible that a light watery solution like percaine can ever reach the higher subarachnoid spaces by direct ascent, in an intelligently conducted procedure. I am convinced that after the adoption of the Trendelenburg position of 10° to 15°, when using percaine, it is quite impossible for the light mixture of percaine and cerebrospinal fluid which has been allowed to ascend to a certain level beforehand, to diffuse any higher. The evidence of mock analgesia is very much against the question as to whether diffusion proper does or does not occur within the spinal canal. Diffusion proper is a very slow process in the absence of disturbing currents, a process taking hours and days. In spinal analgesia we are dealing in seconds and minutes. Mixing and rapid absorption are also taking place to assist in preventing spread to ultra-high levels. With regard to the question of currents: These manifestly will be more likely to arise in rapidly travelling solutions, e.g. rapid and rough methods of injection; very light solutions, especially alcoholic; in cases where a light solution is allowed to ascend up one side of the canal as a peripheral stream with little chance of much mixing and alteration in its density. In the

technique of vertical ascent, using slowly injected percaine, a slow, steadily rising and well-mixed area travels up the whole width of the spinal canal and the absence of marked currents is a strong feature.

A Few Experiments.

Many of the illustrations are based on the appearances presented in the cinematograph film of experiments in progress.

The mixing problem.—Mock experiments soon show an obvious tendency for the injected solution not to mix. Two simple illustrations are given. When percaine 1·003 and a hyperbaric solution 1·010 are injected separately into a canal placed at an angle of about 30°, the percaine rises via the dorsum of the tube and collects at the top. The heavy solution descends via the ventrum and settles in the sacral canal. These positions will be kept for long periods without diffusion or mixing. When the tube has been inverted the solutions pass each other without any attempt at mixing, and eventually change ends. If six solutions injected in a similar manner and placed in series according to their specific gravity, the exact levels being noted by a mark (see fig. B), and the tube put away for three or four days and then re-examined, it will be found that there has been practically no alteration of levels. Diffusion is too slow a process to be heeded much, and this at times in spite of currents. To get mixing to occur two good methods are available. (1) The usual method of allowing a fluid to travel along one side of the canal and making it cross to the opposite side by turning the tube over. This is well illustrated in the cinematograph film. (2) Allowing a light solution to ascend up the vertical canal is the best method of mixing. It rises steadily and slowly, getting more sluggish in the higher reaches because it is mixing every centimetre of the way with the heavier cerebrospinal fluid.

Rate of ascent.—The rate of ascent of a hypobaric solution can be estimated, but in order to get consistent results any factors influencing this rate must be inquired into. These will be discussed in the following order: (*a*) angle of inclination, (*b*) amount injected, (*c*) method of injection, (*d*) effect of temperature, (*e*) variations in specific gravity, (*f*) behaviour of alcoholic solutions. These effects are well demonstrated by mock spinal analgesia in glass tubes, and may be carried out also in a recent dead body. The proof of their value is confirmed by theatre experience.

Angle of inclination.—Carried out in one case with the tube vertical, and in the other with the tube at angle 45°. In the same period of time ascent at an angle is much more rapid than ascent in a vertical tube. This is a very important experiment and easy to confirm. The reason for a slower ascent in the vertical position is concerned with better mixing, resulting in the light solution becoming heavier and heavier as it ascends the canal. Percaine under certain conditions reaches the high-block level in 40 seconds in the vertical canal, thereafter it travels much more slowly, in fact it is slowed up by four or five times in the cervical region as compared with its initial rise in the lumbar region. There can be no question of the safety of the vertical position when the operator knows the ascent rate of percaine or similar hypobaric solutions.

Amount injected.—I propose to say little about amounts, as it is obvious that the greater the amount injected the more rapid will be the rate of ascent. Roughly speaking, doubling the dose nearly doubles the rate of ascent. There is little practical difference however when the amounts do not differ widely: little difference is seen between, say, 10 and 12 c.c. of percaine.

Method of injection.—Rapid injection of a solution gives a wider local field of mixing in the vertical position, and tends to extend further down towards the sacral canal. The impetus given to the fluid allows it to reach the low-block level more quickly. The converse is the case with the slow injection. Once the syringe impetus is removed, however, the slowly injected solution travels rather faster than the rapid one. The reason again lies in the question of mixing. In the vertical

canal barbotage appears as a disappointing method, if it be hoped by this means to push a solution rapidly up to high levels. A slow injection arrives there just as rapidly, if not sooner. As the calculation of rate of ascent must depend on uniformity, any rapid or erratic method of injection must be discarded, apart from their other possible drawbacks. In all cases the injection is carried out by a continuous, slow action.

Temperature.—The following simple facts draw attention to this important factor in the rate of travel of a solution. (*a*) A stovaine-glucose solution (1·010) lying cold in the sacral canal of a glass tube containing similar cold cerebrospinal fluid can be made to rise up the vertical canal by the heat of the hand. (*b*) Percaine (1·003) if injected very cold into a vertical warm tube and cerebrospinal fluid will sink towards the the sacral canal. In other words, it is forgotten that a solution is only at its stated specific gravity at a certain temperature. Cold makes it heavier, and warmth makes it lighter for the time being. By heating a stovaine-glucose solution sufficiently after injection it may be made to rise up the canal. Conversely, if percaine be chilled enough it will act temporarily as a heavy solution. Temperature forms a very important factor then in estimating the rate of travel of a hypobaric solution, for cold will delay or slow the ascent, warmth will accelerate it. In actual practice the exact temperature of the percaine does not matter so long as it approximates the patient's temperature, i.e. between 97° and 99° F. Should the case on the table have a temperature of 103° F. the solution injected should be as near this as possible. In this way we may expect to get uniform results. Very cold percaine injected into a warm solution tends to sink and, as it slowly warms up, it rises by a piecemeal method, by streaks and puff-balls, producing a very irregular effect. This may well explain cases of patchy analgesia.

Specific gravity.—The effect of this is obvious on the ascent rate. The lighter the solution the more rapidly will it ascend. In the film three tubes were shown being injected—percaine, a 25% alcohol solution, and an isobaric solution being used. The behaviour of each and the ascent rates were shown by clocks. It is only desired to point out that if percaine takes a certain time to travel 13 inches, this rate only refers to hypobaric solutions having the same specific gravity, e.g. 1·003. Spinocaine in the same dose would move more rapidly.

Alcoholic solutions.—As the technique to be mentioned concerns the use of hypobaric percaine, a non-alcoholic solution, I propose to be brief on the subject. Alcohol lightens a fluid considerably, and it may be expected to ascend more rapidly if used in the same dosage as percaine. 2 c.c. of spinocaine travels up the vertical ,glass canal at about the same rate as 10 c.c. of percaine. Alcoholic solutions tend to cause great disturbance and currents in a watery fluid, and it is possible that a strong current may carry the solution to higher levels than is expected, in spite of a slight Trendelenburg, thus at times showing signs of uncontrollability. The rise of an alcoholic solution is in great contrast to the steady regular ascent of percaine.

SUMMARY.

The vertical spinal canal offers an excellent method of mixing, for the quiet and steady rise of hypobaric percaine. The rate can be estimated to the low, median and high levels, distances of 6, 9 and 13 inches in a person of average height. A uniform technique is necessary for accuracy, i.e., certain dosage, slow injection, equable temperature of percaine. The vertical position is a perfectly safe posture if the percaine is timed; further ascent is prevented instantaneously by the Trendelenburg position.

The Actual Technique.

Apparatus.—20 c.c. ampoule of percaine, 1 : 1,500 solution, specific gravity 1·003. 1 : 2,000 percaine having a similar specific gravity is often used for operations of

shorter duration; 20 c.c. syringe with nozzle to fit lumbar-puncture needle. The needle used should be of fine calibre, not too rigid, short-pointed but not too blunt. A small gallipot to hold the percaine out of the ampoule; a dish containing faintly acidified water at a temperature of 100° F. Into this the syringe, ampoule, needle and small gallipot are placed for a few minutes before the patient arrives. A tiltometer to give the Trendelenburg angle of 15° (always very difficult to guess); sterilized gloves; hypodermic syringe with one very fine needle for local analgesia of skin and subcutaneous tissues and lumbar aponeurosis; a longer needle for further analgesia of the deeper tissues, especially the region near the laminæ—this needle also gives the operator the line for the lumbar-puncture needle, in those cases where the spinous processes are difficult to see or palpate. Intravenous saline apparatus; ampoules of scopolamine gr. $\frac{1}{100}$ and gr. $\frac{1}{200}$ (without morphia), atropine, ephedrine (usually gr. $1\frac{1}{2}$); coramine (5 c.c. ampoule); carbon dioxide and oxygen. The anæsthetist must be prepared to give an inhalation anæsthetic should this become necessary. The operating table must be capable of easy and immediate adjustment. Some form of handcuff for the patient's forearms and wrists, such as a square piece of canvas on which the patient lies, with broad straps each side for the forearms and wrists. An anæsthetic screen is sometimes necessary. An adjustable trolley to allow the return of the patient in the head-down position to a similar position in bed, blocked at the foot. Failing such a trolley, it is better to use the canvas stretcher for conveyance when the position can easily be maintained.

Preparation.—As for general anæsthesia, glucose being given up to within two hours of operation. A simple sedative the night before. Lumbar skin is prepared at the same time as the operation field. In spinal analgesia the importance of asepsis cannot be overstated. It is unwise to trust to a single dab of iodine before lumbar puncture. One hour before operation the patient is placed comfortably on the theatre trolley, the room darkened or the ward patient screened. The ears are plugged with cotton-wool and the average person receives scopolamine gr. $\frac{1}{100}$ intramuscularly. It is desired to produce, if possible, not deep sleep from which the patient cannot be roused, but that state of somnolence in which there is a loss of fear and very imperfect realization, or none at all, of what is taking place. Talking to and touching the patient is avoided as much as possible. It is often necessary to give a second dose gr. $\frac{1}{200}$ scopolamine, half an hour later. On rare occasions I have delayed the operation for a few minutes for a third dose in resistant cases. Everything is made ready in the theatre so as not to keep the patient waiting. The patient is then raised to a sitting posture across the table and leans comfortably forwards supported by a nurse. The local analgesic is inserted. The 3rd lumbar space is punctured and when cerebrospinal fluid appears, the stylet is reinserted and the needle is pushed a couple of millimetres or so further into the canal by a corkscrew movement. The nurse now makes the patient quite upright, the slow injection is commenced (about 15 seconds for 10 c.c.) and at the same time the seconds-hand clock is started. A certain number of seconds are allowed to elapse *before* the patient is put into the dorsal position; this change of position is carried out rapidly and at the same time the table is being sloped head down to an angle of 15°. It is clear that team work is necessary for this part of the procedure. In order therefore to avoid any delay or misunderstanding, each nurse is told beforehand what she has to do. Average doses and times, for operations lasting about an hour, are as follows:—

Low spinal,	10 c.c.	percaine (1 : 1,500),	20	seconds	allowed	upright.	
Median ,,	12 c.c.	,,	,,	30	,,	,,	,,
High ,,	15 c.c.	,,	,,	40	,,	,,	,,

As the fluid has to travel 6, 9, and 13 inches it will be seen that percaine in these doses is travelling at the rate of about three seconds to the inch. Mention should have been made of the injection of ephedrine gr. $1\frac{1}{2}$ given intramuscularly ten

minutes before lumbar puncture. After three minutes or so at angle 15°, I raise the patient 5° and he is kept at a 10° slope for the remainder of the operation. It is wise now to have the head and neck slightly but definitely hyperextended. It is quite unnecessary to turn the patient when using the vertical method. I have been asked if it is not dangerous to use the vertical position for induction on account of the fall in blood-pressure. The answer is that there is no fall in blood-pressure in such a short period as forty or more seconds. The pins-and-needles effect in the legs is usually not even evident until the patient is comfortably in the dorsal position. The doses mentioned are average ones and suitable for most cases. I have used 6 c.c. for low block and have obtained high block with 10 c.c. The method lends itself to a reduction in dosage. Smaller doses, however, are not recommended until the technique is mastered.

With regard to the timing of the ascent, I would again emphasize that a failure to reach the required level of analgesia is due to the solution being injected *too cold*.

Forty-six cases have been anæsthetized to date by the vertical ascent method and I am satisfied that the technique is simple, safe and sound. Sixteen of these cases were high blocks for operation on the gall-bladder, stomach, duodenum, ureteric calculus, intestinal obstruction, including one case of lumbar sympathectomy. The great majority of the remaining 30 cases were median spinals in connection with lower abdominal operations. The results of this technique have proved eminently satisfactory.

[I am indebted to the Curator of the Museum of the Royal College of Surgeons for permission to examine many specimens and skeletons, and to Professor Woollard for the preparation of the half section of the cadaver, seen in the cinematograph film.]

Section of Obstetrics and Gynæcology

President—W. BLAIR-BELL, F.C.O.G.

[*November* 17, 1933]

DISCUSSION ON THE INVESTIGATION AND TREATMENT OF THE TOXÆMIAS OF PREGNANCY

Dame Louise McIlroy: The subject of toxæmia in pregnancy is of great importance, as we are so conscious of our limited knowledge not only of the metabolic processes of normal pregnancy, but also of the pathological changes which take place as the result of functional deficiencies in the maternal organism. We now realize, however, the enormous influence of toxæmia upon maternal and fœtal mortality.

Maternal mortality.—The London Committee on Eclampsia found that the total mortality of the cases investigated was high (22·1%). The greatest number of deaths were of patients in whom convulsions occurred after labour was over. Toxæmia is a danger, as it is responsible also for hæmorrhage before and after parturition in a number of cases. It is a predisposing factor in puerperal sepsis, urinary tract infections and puerperal insanity.

TABLE I.—MATERNAL MORTALITY IN THE ROYAL FREE HOSPITAL FOR TEN YEARS.

Number of patients 12,085. Number of deaths 35. 2·8 per 1,000.

Sepsis ... —	22·8 per cent.
Toxæmia and eclampsia	20 ,, ,,
Hæmorrhage and obstetric shock ...	31·3 ,, ,,
Heart disease	5·7 ,, ,,
Pulmonary embolus	5·7 ,, ,,
Bronchopneumonia	5·7 ,, ,,
Nephritis, cerebral hæmorrhage ...	2·8 ,, ,,
Acute appendicitis	2·8 ,, ,,
Acute pulmonary œdema ...	2·8 ,, ,,

Maternal disablement.—During the past few years the ill-health among women who have had toxæmia has been ably investigated by Blair-Bell, Young and Gibberd.

I am indebted to Miss Rodway for the investigation of the after-results of 50 patients who had toxæmia in their pregnancies.

TABLE II.—MATERNAL DISABILITY.

Follow-up history of 50 cases of toxæmia.

Primiparæ (34).

No history of previous renal complications.

Good health	18
Chronic nephritis	2
Raised blood-pressure, no albuminuria	9
Raised blood-pressure, albuminuria	1
Headaches and giddiness, no albumin, blood-pressure not raised ...	4

Multiparæ (16).

(a) *No history of renal complications at previous pregnancies.* 6 *cases.*

Good health	1
Albuminuria, ? chronic nephritis	2
Raised blood-pressure, no albuminuria ...	2
Headaches	2

(b) *History of previous renal complications.* 8 *cases.*

Chronic nephritis	2
Raised blood-pressure, no albuminuria but general debility ...	4

Fœtal mortality.—The waste of fœtal life is almost incalculable; it is more marked, however, in cases of renal damage. In toxæmia the greatest danger is to the mother; in chronic nephritis fœtal death is not infrequent.

TABLE III.—CAUSES OF STILLBIRTHS, 1927-1931, ROYAL FREE HOSPITAL.

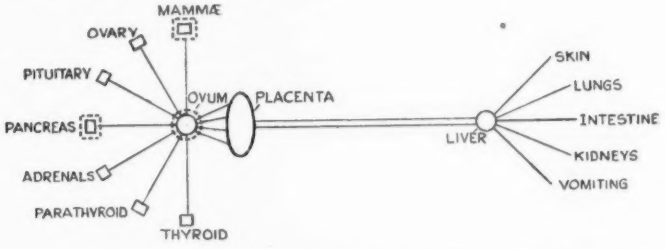
	Approx.
Maternal toxæmia	24%
Obstructed labour, injury at birth ...	20·5%
Placenta prævia	9·7%
Renal disease	9·4%
Prematurity or unknown causes	9·4%
Breech	8·5%
Maternal heart disease	7%
Prolapsed cord	5·5%
Syphilis	4%
Diabetes	2·5%
Ruptured placental vein	1%

Early pregnancy.—The investigation of early pregnancy toxæmia is of the greatest importance, as it is only in this way that we will be able to prevent the serious conditions which occur in later pregnancy. In order, however, to save time it would be more convenient to discuss here the possible sources of toxæmia throughout pregnancy.

Toxæmia is not a marked feature of pregnancy between the sixteenth and thirtieth weeks. This seems to be a period where the maternal and fœtal metabolic relationships are better balanced. The beginning and the end of pregnancy concern us most in our campaign against toxæmia.

I pointed out some years ago[1] that the ovum might be looked upon as a temporary endocrine organ. It settles down amongst the maternal organs and, if it adapts itself to its surroundings and to the other endocrines, the pregnancy is normal in character. If, however, the physiological balance is upset, the subsequent career of the ovum is associated with trouble. Great activity of the endocrines takes place during early pregnancy, and this has an influence more especially upon carbohydrate and calcium metabolism.

Morning sickness, which occurs in about 50% of cases, may be taken as evidence of nature's attempt at balancing the new element with its surroundings in the way of providing an extra channel of excretion.



The following have been suggested as possible ætiological factors in toxæmia:—

(1) *A toxic ovum* associated with abnormal decidual reaction. Hormones are poured into the blood-stream. Fragments of early syncytial formation may also pass through together with the products of protein autolysis. This is all very suggestive as a solution of the problem, but it is somewhat vague. The virulent ovum poisons the maternal tissues, and acts more or less as a parasite. Its action, however, can be curtailed to some extent by the filtration function of the placenta.

[1] "The ovum as an internal secretory organ," *New York Med. Journ.*, 1922.

together with the detoxicating power of the liver and blood. The toxins when neutralized are excreted without damage to the maternal tissues.

(2) *Defective maternal excretion* is due to previous renal damage, usually in multiparæ; it is rare in primigravidæ. Chronic intestinal stasis is an important factor in the prevention of elimination. When nature discovers a defective excretory apparatus she hurries up the process of elimination of poisons by putting on vomiting as a rapid excretory function. Pregnancy is a test of renal efficiency, and the breakdown is, as a rule, early. The more experience I have in the management of the toxic complications of pregnancy, the more I am convinced that our attention should be chiefly directed to the investigation of lowered renal function, together with that of faulty intestinal elimination.

(3) *Deficiencies in diet* are responsible factors. The fœtus in later pregnancy requires a considerable supply of mixed substances such as iron, calcium and glycogen. If this supply is not kept up by dieting the mother, the fœtus drains her tissues for its own imperative requirements; hence there is softening of the teeth in pregnancy. Carbohydrate deficiency causes acidosis and other hepatic derangements. Absence of sunlight and fresh air are responsible for vitamin deficiency.

(4) *Defective endocrine secretions* are of importance as a cause of toxæmia. Our successful efforts to supplement them by glandular extracts such as those from corpus luteum, thyroid and the anterior lobe of the pituitary are proof of this contention.

(5) *Septic foci* such as teeth and tonsils play a part in toxæmia.

(6) *Anxiety neurosis, or fear*, is of the greatest importance. It is difficult to elucidate. It is mainly to be found among primigravidæ and early in pregnancy. The patients, themselves, may be entirely unconscious of its presence. It is the predisposing cause in the majority of cases of vomiting of early pregnancy, which in turn may give rise to acidosis and serious toxæmia. Treatment by rest and isolation and the assurance of safety gives most successful results. Again and again one has the experience of the cessation of severe vomiting after isolating a patient, and the almost immediate recurrence of the symptom when she returns to her home surroundings.

I have omitted such obvious reflex causes as displacements of the uterus.

(7) *Placenta and hepatic function.* — Beyond these more or less ætiological factors in toxæmia in early pregnancy, we have to consider deficiencies in function on the part of the placenta, the liver and the blood. This is more important in the consideration of later pregnancies. If the placenta is a defective filter for the passage of toxins from the fœtus to the mother, or perhaps vice versa, the results are serious. Changes in the placenta, such as infarctions and necrosis, causing loss of function, separation, and hæmorrhage, may be due to toxins from the fœtus. Primary placental changes, themselves, may lead to the production of toxins. The liver becomes overworked in its detoxicating capacity and breaks down, with degeneration of its cells. The result is the circulation of protein poisons and substances such as bile in the blood-stream. If neutralization from the carbohydrate diet is not forthcoming, the result may be fatal.

There is always a tendency to acidosis in every pregnancy, slight though it may be. The blood in toxæmia may be deficient in hæmoglobin and its alkaline reserve tends to be reduced. There are changes in the nitrogen content of the blood. Vomiting is the most frequent symptom of early pregnancy toxæmia. The other most frequent symptom is a tendency to abortion.

Dr. Pillman Williams has recently published in the *Lancet*, 1933 (ii), 858, an account of her investigations into the cause of often-repeated abortions in apparently healthy women. She found that, on examination of the blood, the sugar tolerance test in 90% of these pregnant and non-pregnant patients was lowered. The sugar leak was estimated in the urine. By spacing with small very frequent carbohydrate meals instead of infrequent large meals, the patients were enabled

to continue their pregnancy to term. Dr. Pillman Williams states that a very considerable percentage of cases are related, not to any failure of nitrogen metabolism but to gross errors in carbohydrate metabolism, a fact which is not sufficiently appreciated. These patients did not leak sugar on ordinary diet. Their fasting blood-sugars were either normal or only moderately raised. She considers that the underlying cause of the lowered tolerance for glucose is related to a lack of balance of the ductless glands. Insulin was administered in a few cases. The administration of antuitrin has shown us that abortions can be prevented and is a further proof of the influence of the endocrine organs.

(8) In later pregnancy we have to consider *raised intra-abdominal pressure* as a factor in the causation of toxæmia. The increasing needs of the fœtus and the greater excretion of waste products are not the only cause—in cases of twins—so frequently associated with toxic symptoms in the mother. Hydramnios also by its bulk is associated with great rise of the intra-abdominal pressure.

The symptoms of toxæmia are all well known. Persistent headache is always a matter of concern, and hypertension has a more serious aspect in early than in late pregnancy. Heartburn is a symptom which should never be ignored. In the investigation and treatment of toxæmia we must have the co-operation of the biochemist. It is impossible to have any accurate estimation of the condition without a thorough analysis of the blood and urine at frequent intervals. The biochemist assists us to make a diagnosis of kidney damage if that is present. There is the kidney in chronic nephritis and the kidney which remains healthy under ordinary conditions of life but fails to stand the test of pregnancy. Albumin in the urine may be a symptom of great diagnostic value but some of the fulminating types of eclampsia do not manifest this danger signal until convulsions have occurred.

Œdema has been shown, in cases of chronic nephritis, to depend to some extent on protein starvation. Patients improve rapidly on a protein diet. This may also apply in some degree to toxæmia. In vomiting cases I always try to get the patient on to a mixed diet as soon as possible. If there is a marked protein leak as in albuminuria the tissues require its replacement. Sodium chloride retention as a cause of œdema, may be counteracted by giving a salt-free diet.

I leave the biochemists to discuss the values of the different blood and urine nitrogen partition tests. I am grateful for the help given me by Dr. Pillman Williams and Dr. Rodway in the diagnosis and treatment of cases of toxæmia and of renal deficiency.

Treatment of toxæmia in early pregnancy.—In the discussion of the causation of toxæmia, I have more or less intimated the line of treatment to be followed. It consists mainly first, of elimination, to make up for defective excretion by means of baths, colon lavage, enemata, etc., and secondly, of the dilution and neutralization of the toxins by fluids, and later, by proper dieting. The diet should be mixed, and should consist of green vegetables such as salads, fresh butter, fish and chicken. In many cases in order to get a more rapid response, the diet has to be supplemented directly by calcium, glucose or alkalies. In the cases of anæmia, marmite or cooked liver is given, if proteins are not absolutely contra-indicated.

Sunshine, either natural or artificial, is excellent. The best sedatives are rest in bed and freedom from anxiety.

If the progress of the patient is disappointing, surgical interference may be necessary. In the severe vomiting of early pregnancy, if improvement does not take place within three or four days, induction of abortion was formerly advised. It is rarely necessary nowadays. Why should the deadly hyperemesis be given such prominence in textbooks? It is a very rare condition. When it does occur the uterus should be emptied without delay.

TABLE IV.—ABORTION AT THE ROYAL FREE HOSPITAL.

	Per cent.
Pulmonary tuberculosis	23
Heart disease	17
Nephritis	8
Toxæmia with dead ovum	8
Toxæmia with living ovum	5
Pyelitis	3
A.P.H.	2
Epilepsy	1
Tabes dorsalis	1

In none of these cases was abortion induced on account of vomiting. The so-called cases of toxæmia were cases of hæmorrhage with a dead or macerated ovum.

Surgical interference in early pregnancy is rarely necessary in cases of toxæmia. In chronic nephritis, the operation is advisable in a number of cases. The list of inductions includes cases of rapid and slow induction and of abdominal hysterotomy.

We must remember that in practice a large majority of women are most anxious to continue with the pregnancy. In cases in which the desire for its termination is freely expressed, it is wiser to continue with medical measures only. It is our practice when possible to continue a pregnancy in a case of renal damage and to forbid the occurrence of future pregnancies.

Treatment in late pregnancy.—In late pregnancy the condition is somewhat different. There is less of the element of anxiety neurosis and much more of metabolic disturbances. Induction of premature labour is essential in some cases for two main reasons. If the mother's life is spared but if the toxæmia is prolonged the ultimate damage to the liver and kidneys is very serious and chronic ill-health is the result. The acute forms of toxæmia such as eclampsia may not be serious in their end-results. A prolonged condition of toxæmia with or without convulsions has a marked effect on kidney damage. The second consideration is that the fœtus not infrequently dies *in utero* if induction of labour is deferred for too long a time.

It is important to remember, however, that in eclampsia the worst types of cases sometimes are those in which there has been a spontaneous labour and convulsions have only occurred after it is over.

TABLE V.—30 CASES OF ECLAMPSIA IN 8,000 OBSTETRIC CASES IN THE ROYAL FREE HOSPITAL.

Time of onset		Mortality		
During pregnancy ...	8	2 died undelivered		
During labour	6	During labour ...	0	20%
After labour	16	After labour ...	4	

Booked cases 23—of these only 8 attended adequately.
Emergency 7.
5 cases had no symptoms before onset of convulsions.
3 cases had eclampsia at a previous pregnancy.
3 sets of twins—1 mother, aged 14½ years.

On looking through the literature on the treatment of eclampsia and allied conditions, one is much impressed by the results of conservative versus surgical treatment. This is borne out by one's own experience.

TABLE VI.—INDICATIONS FOR THE INDUCTION OF LABOUR, ROYAL FREE HOSPITAL (10 YEARS).

	Per cent.
Toxæmia	23·5
Nephritis	3·0
Eclampsia	3·0
Other indications such as disproportion, pelvic deformity ...	70·5

Cæsarean section seems an ideal method out of the difficulty in cases of severe toxæmia, but in the opinion of the most experienced obstetricians the greater the surgical interference, the greater the risks and the higher the maternal death rate. There is a place for Cæsarean section, no doubt, and it has its advocates. I rarely employ it for toxæmia.

TABLE VII.—INDICATIONS FOR CÆSAREAN SECTION, ROYAL FREE HOSPITAL (10 YEARS).

	Per cent.
Pelvic deformities	72
Heart disease	3·5
Central placenta prævia	3
Tumours	2
Breech with extended legs	1·5
Transverse	1
Rigid cervix	0·5
Eclampsia	0·25
Double uterus and septate vagina ...	0·25

In cases of toxæmia the post-natal follow-up of the patient is essential. In cases where a future pregnancy is inadvisable the patient should always be given advice as to contraceptive methods.

The discussion of chronic nephritis would occupy many sessions, as also would that of the rôle of the colon bacillus in the production of toxic conditions. Is the latter *post hoc* or *propter hoc*? I know not. Mr. Fuller and Dr. Colebrook have opened out to us a new and interesting line of treatment of infective conditions of the urinary tract in the puerperium[1]. We have begun to try the effect of ketogenic diets with success, but wea re somewhat unwilling to surrender the use of alkalies. We are grateful for the useful suggestion to capture the colon bacillus by culturing the urine at the bedside. It would be of interest to know the results of a ketogenic diet in the case of antenatal patients. Its effect upon the fœtus might be somewhat disturbing.

In conclusion I would like to take this opportunity of refuting the loose statements which are made with regard to the failure in the results of antenatal care. If this care is properly carried out by qualified practitioners there is not the slightest doubt that we will in time reduce the maternal death-rate to its minimum.

Take, for example, eclampsia. Out of our 8,000 in-patients in the Royal Free Hospital only 30 had eclamptic convulsions. I may say that the attendance of consultative cases of toxæmia at the clinics is extremely high. Of these 30 cases, seven were admitted as emergencies, and 15 had made very inadequate attendances at the out-patient department. Toxæmia cannot be prevented to a great extent, but in many cases it can be prevented from developing into a serious condition with a fatal ending.

During five years in the Unit, 126 cases of antepartum hæmorrhage were admitted. Only 17 of these were due to toxæmia, the rest being due to placenta prævia. In my experience this form of hæmorrhage is not so frequent as formerly.

We require a revision of our classification of the toxæmias of pregnancy. This might be entrusted to a Committee of the League of Nations.

May I suggest that we take a more optimistic view of toxæmia and drop the term "pre-eclampsia," which conveys the impression that we are in expectation of the patient developing convulsions? Toxæmia of late pregnancy is in itself sufficient. Also, instead of dwelling too deeply upon the direful effects of toxæmia, we should, in our reports, occasionally publish the good final results of antenatal care in the treatment of early pregnancy complications. We must give proof of the belief that continuous and efficient supervision of *every* expectant mother is absolutely essential.

1 *Lancet* (ii), 1933, 735.

Dr. A. A. Osman: I shall confine my remarks to two important clinical features of these disorders, namely, high blood-pressure, and oliguria, and will consider each of them separately, and from quite different aspects, in the hope that a purely medical point of view may be of some interest.

High blood-pressure in pregnancy toxæmia.—I propose to discuss the late results of the pregnancy toxæmias in relation to two forms of persistent high blood-pressure, firstly, that associated with primary disease of the kidneys (other than primary arteriosclerotic disease), and secondly, that in which there is no evidence of past or present primary kidney disease. The former I will call chronic nephritis with hypertension, and the latter, primary or essential hypertension. Now the recent work of Gibberd, Young, Stander, and others, has drawn attention to the frequency with which pregnancy toxæmias, and especially recurrent albuminuria of pregnancy, are followed by chronic nephritis, and this is in accordance with the clinical experience of general physicians who, at least during the past thirty years, have regarded pregnancy and its complications as the most frequent cause of nephritis in adult women of the child-bearing age. More recently still, however, Theobald has analysed the mortality figures from chronic nephritis in married and single women between the ages of 20 and 55, finding, as a result, that there is relatively little difference in mortality between these two groups and he concludes from this and other evidence, that child-bearing has very little causal association with chronic nephritis. This view is so directly opposed to all clinical experience whilst the evidence upon which it is based would seem to be so sound, that clearly we must still regard the whole question of the possible causal relation of pregnancy and the pregnancy toxæmias to chronic nephritis as *sub judice*.

Although I think it fair to claim that it was the general physicians such as Rayer (1840), and Bartels (1877), who first recognized the possible or probable relation between pregnancy toxæmia and chronic nephritis it must be admitted that they either kept their observations to themselves or were for the most part content with vague published statements of their belief. At any rate such accurate knowledge as we possess on the subject is mainly due to the careful work of their obstetrical colleagues, chief among whom are those whose names I have already mentioned. The method of approach used by these workers was naturally the one most ready to hand, namely to follow up cases of pregnancy toxæmia and see what proportion of them subsequently developed chronic nephritis, or alternatively, as Professor Theobald has done, to compare the mortality figures amongst the relevant sections of the population. Whilst pondering these matters it occurred to me that it might be of interest to know what information could be gained by tackling the problem from another angle and instead of selecting cases of pregnancy toxæmia and studying their subsequent fate, to take a series of cases of "chronic nephritis" in women of suitable age, and endeavour to determine from their past history the probable cause of their chronic nephritis. This method is open to the most obvious objections for the purposes of accurate work and, beyond saying that, for what they are worth, the results suggest a very close causal relation between pregnancy and the pregnancy toxæmias and chronic nephritis, I do not propose to pursue this aspect of the subject further to-night. It was, however, whilst collecting the figures for this little investigation that it became borne in on me that a considerable number of patients referred to me as cases of chronic nephritis following pregnancy toxæmia were possibly not really suffering from this disease at all but from chronic hypertension and that the kidneys were either not primarily affected, or if they were, had since recovered, or were only secondarily involved. Of recent years, and especially since the War, it has become increasingly evident that there is a large number of persons of all races and of both sexes who are the subjects of unusually high blood-pressures. Many of them in all probability do not suffer in any way, are not in need of treatment, and die from other causes. In others, however, life is terminated often prematurely and

as a direct result of continued high blood-pressure in one of three ways, namely heart failure, apoplexy, or renal failure, and in that order, though the last accounts for only about 5% of the deaths among patients with high blood-pressure. By renal failure, of course, one means that so much kidney substance has been destroyed by the essential morbid process (in this case a widespread arteriolosclerosis including, but not confined to the kidneys) that life can no longer be supported. It is evident that there are, and must be, numerous cases in which minor degrees of renal involvement have taken place, revealed by perhaps a slight albuminuria, in which the patient will eventually succumb to myocardial insufficiency, or perhaps a cerebral hæmorrhage. Such cases seen earlier in their course will present themselves with high blood-pressure, with or without headaches or other symptoms, and having a little albumin and perhaps a few casts in the urine. There may at the same time be evidence of structural changes in the arteries elsewhere in the body, such as in the retinal arteries, yet renal function is intact and there is not yet, and may never be, any disturbance of nitrogen metabolism. Such cases were formally all classed as chronic nephritis. We know now that many of them never had any inflammatory or degenerative disease of the kidneys other than that brought about secondarily by vascular disease, and it is customary to refer to them as cases of essential hypertension. It is certainly a condition tending to appear in the latter half of life, whereas true nephritis is essentially a disease of youth. Generally speaking persistent high blood-pressure in persons under 30 years of age is due to or is associated with primary nephritis ; after 30, primary or essential hypertension becomes a greater and greater possibility. There are, of course, numerous cases in whom it is quite impossible during life or even at autopsy, to be certain as to which of the two conditions is present. It should be noticed that the age incidence of essential hypertension is usually given as from 40 to 60 years, though it is not very rare between the ages of 30 and 40, and 60 and 70, and in one particular variety of essential hypertension known as the "malignant hypertension of Fahr," characterized anatomically by necrosis and endarteritis of the arterioles, which occurs at an earlier age, generally between 30 and 40, but often before. This is a comparatively rare condition probably comprising not more than 2% of cases of essential hypertension, but for reasons which will be discussed later, it may well prove to be an important syndrome in connexion with the investigation of the pregnancy toxæmias.

In passing, it may be mentioned that the cause or causes of essential hypertension are entirely unknown. Heredity and a tendency to obesity are certainly disposing causes, diet and mental stress have been blamed, but are of less certain import. Opinion varies as to the relative frequency of essential hypertension in men and in women, though in the latter it is discovered so often at, or just after, the menopause, that an endocrine origin is at once suggested. This, too, is a point to which I shall refer later.

Tho accompanying tables give an analysis of the last fifty cases of so-called "nephritis" in women between the ages of 25 and 45 inclusive, referred to me either in hospital or in private practice. The number of cases is too small to enable one to arrive at any definite conclusions, and they are merely presented to illustrate the point I am trying to make to-night, and that is, the possible importance of the pregnancy toxæmias as a cause of essential hypertension in certain individuals, or perhaps as an activating cause in those already predisposed.

TABLE I.

Analysis of 50 consecutive cases of "nephritis" in women aged 25-45 years inclusive.

Parous	... ...	42
Nulliparous	... ...	8
Of 42 parous	24 = chronic nephritis	
	18 = essential hypertension	

The probable cause in 24 cases of *chronic nephritis* amongst parous was given as

Pregnancy ...	...	...	10 cases
Infective origin	...	...	10 ,,
Unknown ...	...	...	4 ,,

Of the 10 cases attributed to pregnancy
7 had had a pregnancy toxæmia
3 uncertain of this

Of the 10 cases of infective origin
1 had had a pregnancy toxæmia
4 had not ,, ,,
5 were uncertain

Of the 4 cases of doubtful origin
1 had had a pregnancy toxæmia
2 had not ,, ,,
1 was uncertain

TABLE II.

Of 18 cases of *chronic hypertension* amongst parous women, the probable cause was given as

Pregnancy ...	...	...	16
Infection ...	...	...	0
Unknown ...	...	...	2

Of the 16 cases of chronic hypertension attributed to pregnancy
11 had definitely had a pregnancy toxæmia at some time
3 had not, and
2 were uncertain of this

Of the 8 nulliparous
7 had chronic nephritis, and
1 chronic hypertension

Of 50 males of the same ages sent up as suffering from "nephritis," 43 had true chronic nephritis, and 7 essential hypertension.

Now although, both from paucity of numbers and from the obvious fallacies involved in using data obtained by questioning patients, it is not permissible to draw conclusions from these figures, yet I think we are justified in summarizing them and seeing whether they do not suggest a profitable line for further investigation.

First of all, it would seem from these figures that in women of this age-period, at least among parous women, chronic hypertension is almost as frequent as chronic nephritis, namely, as 18 is to 24. Now I am not prepared to assert that all cases I have here labelled as essential hypertension on clinical and biochemical grounds will, if followed for longer periods, or to the end, ultimately prove to be such. Some of them, if seen later, will possibly give a clinical or histological picture typical of chronic nephritis. Nevertheless, I submit that in all probability a high proportion of them will not, and that essential hypertension will come to be recognized as a more important and more frequent aftermath of pregnancy toxæmia than heretofore. Certainly at present one sees not a few cases of post-pregnancy "nephritis" (so-called) in a very advanced stage, or even dying therefrom, in whom the chief clinical features are those of cardiovascular disease and high blood-pressure without sufficient nitrogen retention to cause death. Now, if these cases are not examples of essential hypertension with perhaps some secondary renal involvement, insufficient in itself to cause death, then they must be examples of primary chronic nephritis in which the only prominent sign or symptom has for some years been an abnormally high blood-pressure with or without slight albuminuria. Though such cases are known to occur amongst males, as after war-nephritis, for example, they are certainly comparatively rare. My contention is that pregnancy, or at least pregnancy toxæmia, may well prove to be an important predisposing factor in the production of essential hypertension in some women, or that pregnancy and its complications bring out a latent tendency to essential hypertension in those predisposed.

Of recent years interest has been aroused in the possible relation between disturbances of endocrine function in pregnancy and the pregnancy toxæmias. You are all aware of the work of Anselmino and Hoffmann, who claim to have found a substance in eclamptic blood having the properties of post-pituitary gland secretion, and, as a link between this work and the cases I have been discussing to-night, I would like to draw your attention to a remarkable case described by my colleagues, Drs. Close and Bishop, in a recent number of the Guy's Hospital Reports. This was a case of a basophil adenoma of the anterior lobe of the pituitary gland in a young woman aged 21, and gave rise to what is now known as "Cushing's Syndrome," after its discoverer. The chief features of this syndrome are the occurrence of adiposity, sexual hypoplasia, persistent high blood-pressure, hirsuties, and the presence of albumin, sugar, and a few casts, in the urine. In the later stages there may be nitrogen retention.

In this connection I would like to draw your attention to an article by Harvey Cushing, in the *American Journal of Pathology*, 1933, in which he presents suggestive evidence that the high blood-pressure of both eclampsia and essential hypertension is an expression of functional hyperactivity of the posterior lobe of the pituitary represented anatomically by an infiltrative basophilia of the pars nervosa.

In concluding these remarks on the apparent association between the pregnancy toxæmias and essential hypertension, I am anxious to make it clear that I do not consider the evidence brought forward to-night as justifying the conclusion that there is a direct relation between the two conditions. I merely submit that the possibility calls for further investigation.

Oliguria and its treatment in the pregnancy toxæmia.—I have now had the opportunity of seeing some half dozen cases of late pregnancy complicated by albuminuria, and generally considerable anasarca, in whom the output of urine was so low as to constitute a direct menace to life. Most of these cases were examples of eclampsia or pre-eclampsia, but a few of them had chronic nephritis complicated by pregnancy. I think it is now agreed that in these cases the œdema is due to an abnormal affinity for water on the part of the body tissues in general, and to disturbances in the osmotic pressures between blood and tissues, and not to a primary inability on the part of the kidneys to excrete water. In other words, in these cases water is not presented to the kidneys in a sufficient amount, or in a suitable form, for excretion.

Now in most cases of late pregnancy, or pregnancy toxæmia, with oliguria, this is not of vital importance, because the concentrating power of the kidney for substances normally excreted is not seriously impaired, so that, although the total volume of urine passed is small, its concentration is high, and retention of products in the blood is not greatly increased ; the blood urea, for example, is often not raised. In cases of chronic nephritis complicated by pregnancy, the position may be otherwise. Here the concentrating ability of the kidney for all substances may be grossly impaired, and under such circumstances it is imperative that a correspondingly large volume of urine should be passed in order that the total output of waste products should be sufficient. If it be not so, then the blood urea and other blood constituents will rise and true uræmia will result. Now if, in the former cases, i.e. cases of pregnancy toxæmia with oliguria in which the concentrating power of the kidney is not seriously impaired, the oliguria be sufficiently prolonged or sufficiently severe, there may in some cases come a time when, however good the concentrating ability, the volume passed is insufficient to permit of the necessary total amount of extractives being eliminated, and retention of products in the blood will occur, amongst them urea and other nitrogenous bodies, and again we have a condition of uræmia. In this case, however, the uræmia is temporary and not obligatory. Nevertheless it may, and does, imperil life unless dealt with.

So far as my observations go, this temporary uræmia is never sufficiently marked

to endanger life until some further factor arrives and causes an extra load to be suddenly placed on the already overtaxed excretory powers of the organism as a whole. This additional factor is nearly always the onset of labour, and the physical exertion accompanying it. It is therefore of vital importance that an adequate output of urine in relation to the concentrating power of the kidneys in any given case should be procured in the latest stages of pregnancy and should be maintained (and one cannot over-emphasize this point) throughout labour, and for two or three days after. Failure to do so is, I believe, the reason for some of the occasional cases of death occurring immediately after, or soon after, labour in cases of pregnancy toxæmia in which the symptoms before labour were not sufficiently severe to lead one to expect a fatal issue.

With regard to the treatment of oliguria in the pregnancy toxæmias: On a previous occasion, I submitted to this Section evidence as to the value of alkalies by mouth both therapeutically and prophylactically in cases of pregnancy toxæmia, and of nephritis complicated by pregnancy.[1] Further experience in their use in these cases has in no way caused me to modify the opinions expressed then, and whatever may be the ultimate physical or chemical explanation of their mode of action, from the practical point of view, their chief value lies in the fact that they are amongst the most powerful, least harmful, and most certain diuretics we possess. As a means of preventing and overcoming severe oliguria and anuria I believe them to be of unrivalled value, and for this reason alone, they should be given, though with circumspection, in all cases of pregnancy toxæmia in which oliguria is present or is threatened. Furthermore, they should be given in adequate amounts throughout the period of labour, and for a few days afterwards. I do not assert that all deaths from oliguria and anuria can be prevented by their use, because, although in the majority of such cases an adequate output of urine can be obtained, there still remain some rare, and, I believe, hitherto unrecognized cases, in whom, in spite of an output of 100 or more ounces of fluid per diem from the kidneys under the influence of alkalies, such fluid is nothing more than almost pure water, with a specific gravity of 1000·0. In other words, in these cases the kidneys are capable of passing pure water when it is presented to them, but practically nothing else. Such cases are often doomed, because the kidneys have entirely lost their power of concentrating anything.

Mr. J. Bright Banister: My contribution is based upon the consideration of 2,213 cases occurring between the years 1908 and 1932 and distributed over a wide area. These cases are collected from the reports of maternity hospitals in London, Sheffield, Manchester, Edinburgh, Glasgow and Liverpool, with, in addition, those cases which have occurred in my own practice. Lest they should lead to a pessimistic outlook upon this condition of toxæmia of pregnancy let it be remembered that most of them occur in large maternity hospitals which in themselves concentrate the tragedies occurring in a large area of practice. It is therefore not fair to assume that the disease is in general so fatal as these collections of cases tend to suggest. There are among them 1,502 cases of albuminuria occurring in pregnancy and associated with toxæmic symptoms, 115 cases of acute and subacute nephritis—cases of profound toxæmia not associated with convulsions—and finally, 596 cases of toxæmia associated with convulsions to which we apply the title eclampsia.

In all, there were 125 fatal cases, giving a mortality for a toxæmia of pregnancy occurring in the later months of 5·6%. Considering this in more detail I find there are 92 fatal cases of eclampsia giving a mortality rate for eclampsia of 15·4%. In addition there are 18 cases said to be fatal by reason of nephritic conditions primarily, and there are 15 cases in which death is ascribed to acute toxæmia without convulsions. It may be interest to consider the fatal cases of eclampsia in some greater detail.

1 *Proceedings*, 1931, xxiv, 880 (Sect. Obst. 40).

The mortality in eclampsia in this series is 15·4%, and it is interesting to consider what difference there has been in this mortality in recent years. I have divided the series into two twelve-year sections. In the first twelve years there were 206 cases of eclampsia with 36 deaths, giving a mortality of 17·4%. In the second twelve years there were 390 cases with 56 deaths, giving a mortality of 14·3%. Can we hope from this that the management of these cases is improving, and that we are likely to behold an increasing diminution in the death-rate as time goes on?

Cæsarean section as a treatment is always being considered in every obstetric complication, so I tried to discover what sort of mortality followed Cæsarean section as a remedy in this series of cases. I found that 36 Cæsarean sections had been performed, and that 8 of these terminated fatally—the mortality being 17·4%. It is interesting to note that for seven years there has not been, according to this series, a Cæsarean section carried out for eclampsia in any of the institutions whose records I have reviewed. Another interesting point emerges from a perusal of the histories of these deaths from eclampsia, namely that in 30 of them, i.e. 33% of the whole, it is recorded that the delivery was difficult or that manual dilatation of the cervix was practised. This seems to suggest that any great amount of manual interference to effect delivery does not enhance—to say the least—the patient's chance of recovery.

The 15 fatal cases ascribed to acute toxæmia without convulsions are not without interest. In 8 of these there is a history of a prolonged administration of chloroform, and in most of them a difficult delivery. It seems fitting once more to call attention to the danger that may follow a prolonged administration of chloroform in a case of toxæmia complicating pregnancy, although it is given as a routine in Professor's Stroganoff's most successful treatment of the condition. I would like to suggest that it is advisable to be careful in such administration, and to reduce the amount of chloroform given to such patients to a minimum. I think the fact that in 50% of these acute toxæmic cases there should be a history of prolonged chloroform administration is in itself sufficient to make us at least consider the question, and it cannot be denied that poisoning by chloroform does produce post-mortem appearances which are indistinguishable from those of acute eclampsia.

This series also provides evidence of the value of ante-natal care in the prevention of the condition of eclampsia. Unfortunately, up to recent years, cases in the reports of the maternity hospitals have not been divided into "booked" and "emergency," but I have notes of 225 cases occurring since such discrimination was generally made. Of these 225, 20 were booked cases, the remaining 205 were emergency cases. This should be sufficient to show that our insistence upon the importance of ante-natal care is fully justified. In this connexion a statement has been made that eclampsia is a preventable disease. Therefore I considered the fatal cases of eclampsia in reference to the length of time during which those cases showed symptoms before they came under treatment. It may interest you to know that of these 92 fatal cases of eclampsia 33 showed symptoms for less than one week. This appears to me to suggest that the dictum "preventable disease" is harsh, and reflects unnecessary discredit upon the practitioner of obstetrics.

Now may I make a few general reflections on the treatment of these cases of toxæmia of late pregnancy in the light of twenty-five years' experience. First, there does not seem to be any complication of pregnancy in which a careful and detailed consideration of the clinical picture in each case will offer more help in deciding the treatment than it does in this condition. I believe that the investigations of the laboratory should be auxiliary to clinical watchfulness, and should be regarded rather as the servant than as the director of the clinician. Next, I am impressed by the results following the adoption of and perseverance in a purely

medical line of treatment in cases in which the institution of such treatment is followed reasonably soon by definite improvement in the clinical picture. I think it is a pity to adopt an arbitrary time limit during which such medical treatment should be continued. There is too much pessimism shown in the tendency to adopt more radical procedures if at the end of from seven to ten days the patient is not immeasurably better than she was when the treatment was instituted. My own view is that a certain improvement without a recurrence of any untoward symptoms should make it justifiable to continue the expectant medical line of treatment for quite a long time. I would persevere with a patient in whom the blood-pressure remained steadily under 170 mm. systolic, whose urine output remained good, and whose skin continued to act well even when albumin did not diminish or œdema disappear.

Two cases come to my memory at once. One, a patient who in her first pregnancy had a very serious attack of eclampsia, recovering after some six months of illness. Five years later, very desirous of a child and then aged 39, she sought advice and was told that there was a reasonable chance of her going through a second pregnancy successfully. At the third month pyelitis developed. At the fifth month she had quite severe symptoms of pregnancy toxæmia. She was under observation from this time to the thirty-fourth week, during part of which she improved, and during the whole of which treatment had to be varied from day to day, or from week to week, according to her clinical state. At the thirty-fourth week a definite rise in blood-pressure developed, with marked mental confusion and an increase in the amount of albuminuria with oliguria. It was then decided that, having waited so long, the only chance of giving her a live baby was immediate delivery, and so Cæsarean section was performed. The child weighed 3 lb., but throve from the outset and now, four months afterwards, the patient is in very fair health, and is quite of the opinion that the troubles through which she has passed are amply justified by the possession of a perfectly healthy son.

Another woman, also nearly 40 years old and pregnant after eleven years of married life, developed toxæmic symptoms at the sixth month and the most prominent of these was a very marked rise in blood-pressure, which was, when I first saw her, 205. This patient was kept in bed, the usual medical treatment carried out, and for the control of the blood-pressure she had ½ c.c. of veratrone given to her every twelve hours from that until the thirty-seventh week, at which time labour was induced and in thirty-six hours she was delivered of a normal healthy girl. Her subsequent history showed that although she was not in robust health she was at least able to enjoy life and was immeasurably cheered by the possession of her daughter. This occurred about fourteen years ago and the patient is still alive and well.

A totally different problem is presented by those cases in which the introduction of eliminative and purely medical treatment is not followed by any improvement, where a patient is not better but rather grows worse. Here I feel that there is a place for entirely radical treatment. Miss Margaret Basden has done good service to obstetrics in pointing out the value of Cæsarean section in these cases of non-improving pre-eclamptic conditions. I also feel that it is just possible that there may be, after all, a place for Cæsarean section in cases in which eclampsia has already developed. Here one is treading upon dangerous ground, but I cannot help suggesting that if a patient develops an eclamptic fit after eliminative treatment has been used for some time, if her general condition is good, and if the child has a reasonable chance of survival, Cæsarean section should certainly be considered.

The impression gained from reading these cases is that practically every case which is described as profound toxæmia without convulsions ended fatally. Most of these presented the clinical signs of jaundice, persistent vomiting, sometimes with hæmatemesis and increasing coma which often supervened upon a maniacal

state. These cases suggest profound primary disturbance of liver function and serve to strengthen a growing suspicion that a breakdown of hepatic efficiency will profoundly affect the prognosis in the presence of toxæmic symptoms in pregnancy.

Dr. James Young said that Dr. Osman's investigation was of great importance in regard both to the pathology of toxæmia and to the understanding of the factors responsible for the high rate of disability which followed toxæmia. They tended to emphasize also the importance of pregnancy in the causation of cardio-renal disorders generally in adult women. In Edinburgh about 6% of pregnant women suffered from the pre-eclamptic type of toxæmia. In Scotland it was more prevalent and more lethal than in England and Wales, and his remarks must, to some extent, be qualified by this finding. In his experience toxæmia was rarely capable of being appreciably affected by any form of treatment short of the termination of pregnancy. It was either static or progressive so long as the fœtus was alive. The general principles of treatment which he adopted were as follows: If the case was seen for the first time when the child was viable, that is, after the thirty-sixth week, he generally advised termination of pregnancy at once. This was in the interests not only of the mother, but of the child. The risk of intra-uterine death of the fœtus as the result of a continuing toxæmia was, in his opinion, greater than that associated with prematurity at this stage. If, on the other hand, the patient was first seen at a comparatively early stage in pregnancy, say, at the sixth month, he considered that, unless the toxæmia was of the mildest character and was maintained in this category, the pregnancy should be terminated at once. In his opinion the risk of permanent cardio-renal damage to the mother entailed by allowing the pregnancy to continue until viability of the child was assured, that is, over a period of two months, was very great indeed, In cases seen during the eighth month there might be justification for temporizing from day to day in the hope of obtaining a viable child, but it should always be remembered that under these conditions we were gambling with the life and health of a mother on the problematical chance of obtaining a live child. Finally, it was important to recognize the fact that practically all cases of toxæmia required hospital or nursing-home treatment. The constant rest and unbroken vigilance essential in the management of these cases were rarely possible under domiciliary conditions. The toxæmias of pregnancy in this respect were similar to such other complications as ante-partum hæmorrhage and heart disease associated with pregnancy.

Dr. G. W. Theobald agreed with Dr. Young that there was a higher incidence of the toxæmias of pregnancy in Scotland than in the South of England. It followed either that the women of Scotland were less capable of bearing children or that the toxæmias of pregnancy were diseases of environment. He did not believe either in a pregnancy toxin or that the kidney of pregnancy was prone to nephritic changes. He had at the moment a patient under his care who suffered from "kidney trouble" during her first pregnancy, the baby being born dead. She was admitted to hospital, pregnant for the second time, with albuminuria and a blood-pressure of 160/136. She was not confined to bed and was allowed a full diet, except that fish was substituted for meat, and was given in addition iron, iodine, vitamins A, B, and D, and intramuscular injections of calcium gluconate. Her blood-pressure was now 130/86 and her urine was albumin free. In his view the toxæmias of pregnancy were deficiency diseases and could be prevented.

Professor J. Shaw Dunn: The result of a recent investigation by Dr. Dugald Baird and myself, of kidneys from fatal cases of eclampsia has been to confirm the findings of Löhlein and Fahr in Germany and of Bell in America, that there is a

constant renal lesion. This affects the glomeruli, and though it has the appearance of a minor change, it acquires more significance from its universal distribution in all tufts, which permits of its interfering with proper renal functionation. Its features often suggest a process of some duration and for this reason, coupled with the very frequent occurrence of pre-eclamptic renal symptoms, referred to by earlier speakers, we consider that this change in the glomeruli constitutes the structural basis of the common albuminuria, or nephritis of pregnancy. An important negative observation is the frequent absence of definite damage of tubular epithelium, which, so far as it goes, is contrary to the assumption of the presence of a toxin with lethal effects on protoplasm. No evidence can be offered as to the causation of the renal lesion. The main indications of the findings, so far, are to emphasize the importance of an antecedent renal factor for convulsive eclampsia even in the absence of any definite renal history, and to support Fahr's suggestion, that if anything in the nature of a toxin is at work, it is one which can act for a long time, producing only mild renal effects, but which may exhibit sudden cumulative effects at a later period. The common tendency to rise of blood-pressure, either gradual or, in some cases, fairly suddenly, is another suggestive feature to be explained by the hypothetical toxin. Attention to the existence of a renal change may broaden the basis of inquiry for investigators in this difficult field.

Mr. G. F. Gibberd said that he had been impressed by the large measure of agreement amongst the speakers who had stressed the importance of the late sequelæ of the toxæmias—that was to say, chronic nephritis and allied conditions. He was particularly glad to hear the support that Dr. Osman, as a physician, was able to give to the view that permanent cardio-renal damage was a real danger in these cases. Dr. Osman's suggestion that essential hypertension as well as a true chronic nephritis might be caused by a pregnancy toxæmia was an entirely new idea, and would necessitate a revision of some of his (Mr. Gibberd's) cases which had been diagnosed as chronic nephritis, but might really be cases of hypertension with secondary renal involvement. The important fact, however, was that in either case the chronic condition could be looked upon as the aftermath of the pregnancy toxæmia.

Dr. Theobald's criticism of those who used the term "toxæmia" was rather unfair. Everyone admitted that the cause of these diseases was obscure, and to regard them as a manifestation of a "toxæmia" was merely a useful hypothesis. In the absence of a more satisfactory explanation he had found such theories as that which Dr. James Young had put forward in 1914 of the utmost value in guiding his own observations.

It was amazing that until the publication of the work of Professor Shaw Dunn and Dr. Baird, the true nature of the anatomical lesion in the kidney of eclampsia was unknown in this country. He regarded their work as one of the greatest advances in the exact study of the toxæmias that had been made in recent years.

Dr. Horace Evans said that in the course of work in the Nephritis Clinic at the London Hospital he had recently been interested in certain cases of acute nephritis which had exhibited hypertensive encephalopathy. These cases resembled eclampsia gravidarum inasmuch as there was usually a sudden rise in blood-pressure associated with intense headache, fits, vomiting, coma and blindness. Sometimes there was a rapid development of retinal changes. He thought that the mechanism in such conditions was probably vascular and asked whether anyone present had observed spasm of the retinal arteries preceding other retinal changes in eclampsia.

Mr. Green-Armytage said that the idea of no toxin and no restriction in diet was dangerous from the standpoint of every practitioner throughout the Empire. Twenty-five years' experience had shown that in the tropics 15% of primiparæ,

both pure European and indigenous, suffered from the signs and symptoms of toxæmia—frequently with fatal results unless evacuation, hysterotomy, or Cæsarean section were performed. His own view was that if symptoms did not react to treatment and show real amelioration within ten days, for the sake of the mother the pregnancy should be terminated. The orthodox Hindu woman, with abundance of sunlight, and with calcium, iodine and iron in her dietary of vegetables, milk and rice, was just as liable to toxæmia as her sister from Europe whose diet was mixed. It was like beating against the air to say there was no toxin; in his opinion the poison was a histamine allied to that of the colubrine snakes, and until its antidote was discovered by biochemists experimenting, like Harvey, in the Zoo, the toxæmias of pregnancy would continue, on the theory of Dr. Young.

Dr. Osman (in reply): Mr. Bright Banister referred to the danger of giving chloroform in cases of pregnancy toxæmia. In my experience, too, chloroform is a most dangerous drug to use in any case in which the kidneys are already damaged, and particularly in cases of nephritis.

Professor Theobald suggests that unmarried women suffer as much from nephritis as married women, and that therefore pregnancy is not an important causal factor in the production of chronic nephritis. I am not prepared to accept this contention at present. It has always been believed, on fairly good evidence, that chronic nephritis is more frequently met with in males of all ages than in females, and in married women than in single. Chronic nephritis is certainly common amongst young unmarried women, and my clinical impression is that of recent years it has become more so, and is rapidly reaching the male incidence for the same age-groups. Perhaps this is due to the altered conditions of life and the greater freedom of young women, especially since the War. At present there is not sufficient definite evidence to decide this point. I agree with him entirely as to the importance of a full diet throughout in cases of pregnancy toxæmia.

I can confirm the findings of Dr. Horace Evans as to the presence of actual spasm in the retinal blood-vessels in some cases of acute nephritis in children. I have had photographs taken of the contracted retinal vessels for purposes of measurement, and have noticed that during the spastic stage hæmaturia may be much less marked than later, when the retinal vessels are more relaxed. This suggests that there is a simultaneous spasm and relaxation of the renal and retinal vessels. I have no experience of this retinal spasm in pregnancy toxæmia, but it is a point urgently needing further investigation.

Section of Ophthalmology

President—A. C. HUDSON, F.R.C.S.

MEETING HELD AT THE WESTERN OPHTHALMIC HOSPITAL, DECEMBER 8, 1933.

Multipuncture Diathermy Operation.—J. COLE MARSHALL, F.R.C.S.

F. H., female, aged 72.

History of moving pieces of furniture and sudden failure of sight.

Examination.— 13.9.33 : Projecting detachment in upper half temporal quadrant. Retina degenerated. Horseshoe tear.

Operations.—(1) 18.9.33 : *Scleral puncture* 14·15 mm. from limbus. Considerable fluid like vitreous escaped. Carbolic in repositor hole ; though eye softened, retina was not quite back. 22.9.33 : Retina attached ; hole *not* visible. 24.9.33 : Retina re-detaching ; hole now seen. 27.9.33 : retina completely detached.

(2) 28.9.33 : *Scleral punctures.* "Stippling" and diathermy "punctures." 1.10.33 : In spite of patient getting out of bed, retina now back ; scar not seen. 28.11.33 : Retina re-attached ; typical Safar scars ; vision $\frac{6}{24}$ with correction.

Multipuncture Diathermy Operation (Safar's Method). — J. COLE MARSHALL, F.R.C.S.

E. B., male, aged 59. Tailor.

History.—No history of accident since age of 8 years, or of inflamed eyes or injury recently. Two years ago felt that an "air bubble" was floating on upper right corner of right eye.

On examination.—11.1.33 : Main part of detachment was in upper temporal quadrant. Towards the periphery in this region are dots of pigmentation. Just central to the above, at 11 o'clock, there is a horseshoe-shaped tear somewhat in same relation to pigment ; smaller tear at 10 o'clock. Vision : Daylight. Slit lamp : Both corneæ show K. P. spots. Right eye : few cells in anterior chamber. Fields : Failure in upper temporal half of field.

Operation.—16.1.33 : Circle of punctures about 13-16 mm. from limbus. 17.1.33 : Field good to hand ; retina flat. 3.2.33 : Right −8·0 sp.=$\frac{6}{60}$. Field full to $\frac{1}{4}°$ white. 3.3.33 : Vision with glasses $\frac{6}{18}$. 29.9.33 : Everything quite all right ; vision $\frac{6}{18}$; has been working as a tailor.

These cases illustrate the treatment of detached retina by the multi-puncture method with diathermy. I read a paper on the subject in February last. One great advantage of the operation is that you know exactly what you are doing and where you are putting your diathermy point to get the area of coagulation in the choroid. You can go back to any distance you please, by, if necessary, resecting the muscle. A point which Safar himself emphasizes is that the retina is not injured. In the first of these two cases I tried scleral puncture and carbolic, and at the time I thought the treatment had succeeded, but after ten days the detachment returned. Then I did the multi-puncture method of Safar, and the patient is now practically cured, and has vision $\frac{6}{18}$.

Discussion.—Mr. HUMPHRY NEAME, referring to Mr. Cole Marshall's remark that no damage was done to the retina by this operation, said that by using a small electrode by the ordinary diathermy method there was no risk of causing damage to the retina, as the eye was not punctured by it. Probably the heat applied was effective only on the choroid, and the retina did not receive any appreciable heat effect.

Mr. COLE MARSHALL (in reply) admitted that he had sometimes found it difficult to decide when not to operate. If the patient could perceive daylight and there was a definite tear, whatever the age of the patient or duration of the detachment he thought an attempt should be made by the method.

In reply to Mr. Neame, the Viennese school was enthusiastic about this method because cases could be treated by it without a large puncture being made, and especially because it was not necessary to use a trephine. Safar's view was that after the subretinal fluid had been let out and the healthy retina had come back against the puncture, if a trephine, or a knife, or electric cautery was used, trouble with the retina might ensue, and folding or puckering might occur. Professor Weve aimed at not letting the fluid out; he secured drainage out through the multiple punctures.

Splitting of Right and Left Corneæ.—J. COLE MARSHALL, F.R.C.S.

R. C., male, aged 17.

November 1928.—Attended Coventry Hospital. Vision: right, $\frac{6}{12}$; left, $-\frac{6}{6}$. Right eye then inflamed one month. Keratitis profunda and small areas of scleritis.

1931-1932.—Eyes became gradually worse. Case shown at a meeting of the Section in 1932. Both corneæ had brownish-yellowish creamy deposits.

Examination.—Wassermann reaction negative; nothing abnormal found in general health. Teeth, nose and throat normal. Urine normal.

(Fuchs: Ætiology of cases "unknown." Vogt's new book: nothing bearing on case.) Some members said: "Degeneration after interstitial keratitis"; "sclerosing keratitis."

Operations.—Left eye. 26.5.1931: Splitting of left cornea in attempt to remove calcareous leucoma. 20.10.1931: small area of calcareous material scraped off. 9.11.1931: left optical iridectomy no help. *Right eye.*—25.4.32: Splitting and scraping of cornea. 18.9.33: cornea split, contents of calcareous patch scraped with very fine dental burr.

When the case was shown two years ago, Mr. Elmore Brewerton, then President, suggested that I should try to split the cornea and get out the creamy or chalky-looking material, which seemed to be in the layers. This procedure had been very successful in a case of Mr. Brewerton's own, and it had been followed by distinct improvement in vision, but it has not been so successful in this case, though the boy is greatly pleased with what I have done. I dissected up a flap, and with Lister's splitter, I continued to divide the layers until I got to the centre of the cornea. In my last operation I put the finest dental burr along the little tunnel, and whirled the burr round, and yet the eye settled down quietly, and quickly. The case shows that the cornea can be split and the material taken out apparently without any harm resulting or a serious reaction being produced.

Juvenile Glaucoma ? Secondary.—H. J. TAGGART, F.R.C.S.

M. J., a girl, aged 10.

History.—First seen July 1930. Both eyes inflamed, intermittently, for eighteen months previously. Treated at Welfare Clinic.

On examination (July 1930).—Right eye: superficial and deep keratitis. Left eye: superficial keratitis. Wassermann reaction negative. Tonsils septic; removed later.

June 1931.—Keratitis subsided. Vision $\frac{6}{6}$ each eye with low myopic correction.

September 1931 to April 1932.—Recurrent attacks of mild keratitis. April 1932.—Right eye: T + 1 Schiotz 30 mm., slight corneal œdema. Left eye: Tn. Schiotz 25 mm. Both discs cupped, right markedly so. Both fields generally contracted.

April 1932.—Right eye trephined. Convalescence slow—mild iritis and fine K.P.

November 1932.—Right eye quiet: no K.P. Vision, $\frac{6}{9}$ each eye.

May 1933.—No trouble since. Vision $\frac{6}{9}$ each eye. Skiagram of skull normal.

November 1933.—No trouble since. Cupping appears same in each eye. Tn. Schiotz 25 mm., each eye. Fields more contracted. Vision = $\frac{6}{12}$ each eye.

Discussion.—Mr. RANSOM PICKARD said Mr. Taggart had told him that there had been a slightly increased myopia—from 0·25 to 1·25. He (the speaker) had seen, in the last year or two, one or two cases in young people, diagnosed as cases of glaucoma, in which myopia had come on, probably being in the nature of a safety-valve to the pressure. In the present case, though the pressure shown was not high, it would be worth while to trephine again on the right, otherwise the patient might go blind.

The PRESIDENT asked what the experience of members was with regard to the size of the trephine in these cases. If one used a 1½ mm. it was common to find that the trephine hole closed. Much could be said in favour of using a 2 mm. trephine in such eyes, as on the one hand they had great power of repair, and on the other there was an abnormally wide interval between the cornea-conjunctival junction and the periphery of the anterior chamber.

Mr. T. HARRISON BUTLER said that he had been collecting statistics of all his glaucoma cases during the last two years, and he had found that 20% of his failures were due to a complete healing up of the hole. He changed his trephine from 1·5 size to 2, and the change had wiped out that cause of failure, though he was afraid it introduced other difficulties. With the larger trephine there was likely to be a bigger proportion of blebs and the late formation of anterior chamber, and, in some cases, the formation of cataract. Therefore he had now discontinued trephining except in exceptional cases.

Mr. HUMPHRY NEAME said that two years ago he had operated upon a child aged 2 years, who had buphthalmos and some signs of acute glaucoma in both eyes, with a steamy cornea. He trephined with a 2 mm. instrument, and extended the opening with a Holth punch to make the hole 4 mm. long. The child did very satisfactorily; there was now a bright clear cornea, and the mother reported that the sight was good. After trephining in the past one often saw the patient come back years afterwards with the eyes steadily enlarging and the sight deteriorating.

Mr. FRANK LAW said that he did the same thing as Mr. Neame, with good results, but he performed complete iridectomy in each eye.

Epithelioma of Lid.—H. J. TAGGART, F.R.C.S.

O. B., female, aged 35.

First seen November 3, 1933. Had had wart on right upper eyelid for twelve months; snipped off once by own doctor; recurred. Caustic applied; wart again recurred.

On examination.—Small papilloma, size of lentil, growing from lid margin at junction of outer and middle-thirds. No induration or inflammation. Pre-auricular gland not palpable.

November 3, 1933. Growth removed by horizontal wedge resection of base (under novocain and adrenaline). Healing by first intention.

Pathologist's report on microscopical section: Epithelioma with cell nests.

Thus what was an apparently innocent growth is undoubtedly a serious one. I should value the advice of members as to whether radium should be applied or whether I should straightway do a wider resection of the lid followed by a plastic operation.

Discussion.—The PRESIDENT said that certainly the microscopic diagnosis was of great importance in this case, especially in regard to the advisability of further operation, as after extensive removal of the eyelid, the eye was liable to suffer from exposure or irritation.

Mr. D. LEIGHTON DAVIES said he thought that Mr. Taggart should wait to see whether recurrence took place. Usually in cases of lip epithelioma local removal was not followed by recurrence even if a wedge-shaped excision was made.

Marginal Degeneration of the Corneæ.—J. H. DOGGART, F.R.C.S.

This case is shown in order to illustrate the slow progress of marginal degeneration. The patient, a man aged 24, had noticed failure in his left vision since the beginning of 1930. There has been very little change in the appearance of his eyes since he was shown at the meeting of this Section on January 9, 1931.[1] The changes, which are more marked in the left eye than in the right, consist of a marginal vascularized opacity situated on the upper part of each cornea, and sharply limited to the central side by a greyish-white line. This disease begins in one eye, but the second eye is always involved sooner or later. The marginal opacity proceeds to gutter formation, and then to ectasia. When the thinning of the affected area has advanced sufficiently, such eyes may undergo spontaneous rupture.

Traumatic Monocular Argyll-Robertson Pupil.—A. RUGG-GUNN, F.R.C.S.

J. F., male, aged 9. Knocked down by a car last May; was probably unconscious for a short time, and was delirious for some days. He was admitted to the Redhill Hospital, Edgware, and detained for ten weeks. A radiogram showed a fracture of the vault, mainly the right frontal bone. Both tympanic membranes were ruptured, so that there was probably a combined fracture of the base and vault. After the accident all movements of the right eye were paralysed—3rd, 4th and 6th nerves. The levator is said to have been "weak," but apparently ptosis was not complete. There was ecchymosis of the lids, but no proptosis, and, though this is not certain, subconjunctival hæmorrhage.

Distant vision now = $\frac{6}{6}$ right and left; near vision: right < J 12, left = J 1.

The fields are not affected and the fundi are normal. All power of upward movement of the right eye is lost, and there is no accommodation.

The right pupil does not react to light directly or consensually, but reacts on convergence-accommodation. There is no miosis and the pupil is mobile. That is to say, in ordinary daylight it is about the same size as its fellow, contracts on adduction and dilates on abduction. The left pupil is normal.

The site of the lesion: the pupillo-motor light-reflex path leaves the optic tract about its posterior third, avoids the lateral geniculate body, and passes to a relay-station in the superior colliculus by the superior brachium. From the colliculus to the oculomotor nucleus its path is uncertain. There must be a second decussation. Various routes have been suggested, such as the fountain decussation of Meynert and the fibræ radiales of Winkler. If the 3rd nerve paralysis which was present immediately after the accident, was nuclear and the present palsy a residuum, then it is legitimate to infer that the lesion, possibly scattered hæmorrhages as a result of intracranial concussion or jarring, involved the oculomotor nucleus and the adjacent terminal part of the colliculo-nuclear tract. This would explain the present condition.

On the other hand, if the 4th or 6th nerves were also paralysed and the ptosis incomplete, it is more plausible that the condition is a partial sphenoidal fissure syndrome, due to hæmorrhage in the orbit and affecting the ciliary ganglion. This is the opinion of Dr. Blake Pritchard, neurologist to the Hospital, and also, I think, of Dr. E. B. Brooke of the Redhill Hospital.

[1] *Proceedings*, 1931, xxiv, 755, Sect. Ophth. 25.

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Section of Ophthalmology.

Unilateral Proptosis.—A. C. HUDSON, F.R.C.S. (President).

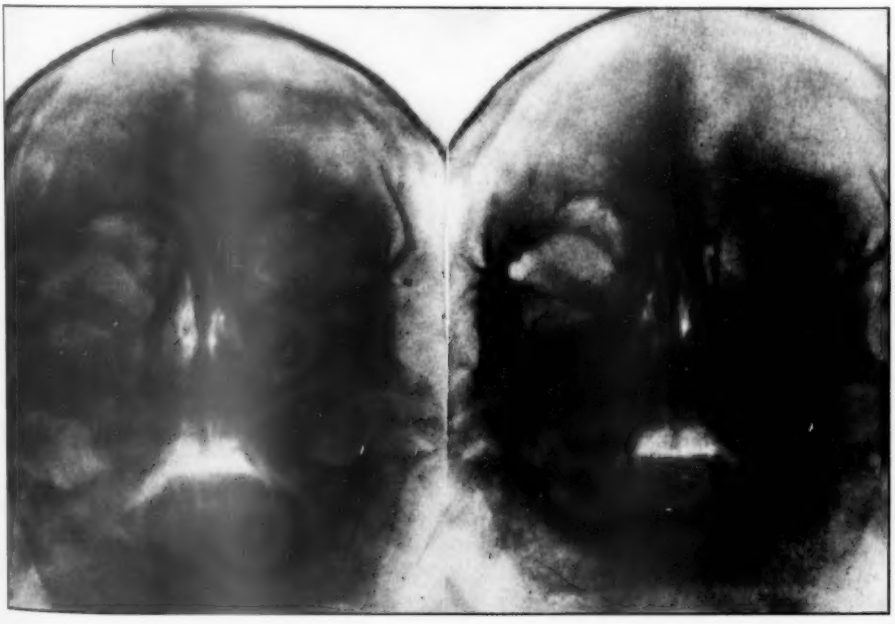
D. R., a boy aged 5.

Prominence of right eye noticed for one year past. Father and mother healthy; no miscarriage; two siblings, both healthy. Patient has had no illness except measles. Wassermann reaction negative. Nose and throat and thoracic and abdominal organs healthy. Blood-count normal. Temperature normal.

The right eye is displaced straight forwards. No limitation of ocular movement no signs of inflammation. Pupil normal; fundus normal. Firm resistance to backward pressure on eyeball. No pain on pressure; no pulsation.

Skiagrams show erosion of roof of right orbit, with some bony hypertrophy. Diagnosis: possibly cavernous angeioma.

STEREOSCOPIC SKIAGRAM



HUDSON: Unilateral Proptosis.

UNIV. OF MICH.

Two Cases of Malignant Melanomata (Multiple) of the Conjunctiva and Eyelids.—A. RUGG-GUNN, F.R.C.S.

(I) G. D. W., male, aged 64. First seen five years ago, when numerous, irregular, deeply pigmented patches were observed in the palpebral and bulbar conjunctiva of the right eye. Patient thought that he had had these since birth. Vision with correction = $\frac{6}{6}$ right and left. Eyes otherwise normal. Seen a year later—patches apparently exactly the same.

In December of last year there was present a jet-black, pedunculated, round growth, roughly 4 to 5 mm. in diameter, attached to the bulbar conjunctiva near the semilunar fold. The growth protruded slightly between the lids when the eye was closed. It was excised and the pathologist, Dr. Hervey Wyatt, reported that it was a melanotic sarcoma. The sections were seen by several others, all of whom concurred in the diagnosis.

On the suggestion of Sir Stewart Duke-Elder, one of the patches, including both palpebral and bulbar conjunctivæ, was excised and submitted to the pathologist, who again reported the presence of sarcoma cells.

The significance of these findings and alternative methods of treatment were freely discussed with the patient and his doctor—Dr. W. J. Dwyer. The patient was averse to operation and volunteered to attend regularly for a fortnightly examination, in order to detect at an early stage naked-eye evidence of activity.

After four or five months, however, his visits ceased. There is now definite overgrowth in several places in the lower fornix and lower palpebral conjunctiva.

(II) H. S., male, aged 65. Attended the Western Ophthalmic Hospital on account of a lime burn of the right cornea. During examination a pigmented nodule, about $\frac{1}{2}$ cm. diameter, involving the skin of the right upper eyelid and the palpebral conjunctiva was discovered. Two or three smaller, flat pigment deposits were present in the same eyelid and exactly opposite one of these was a similar deposit on the lower lid margin. The larger nodule was excised and found to permeate the whole thickness of the lid at its margin.

The pathologist, Dr. Hervey Wyatt, reported that the sections showed a spindle-celled sarcoma with patches of pigment. Both eyelids and the orbital contents were subsequently removed. This case is shown because of its affinity with the other, and because during healing thin superficial flakes of bone repeatedly underwent necrosis, after the patient left hospital, eventually forming sinuses which now communicate with the frontal air sinus and the nasal cavity. I shall be glad of suggestions for dealing with these complications.

These melanomata have been variously described as sarcomata and as carcinomata. The sections from these two cases lean to the sarcoma type. As a rule, however, at the present time these growths are classed among the carcinomata. A curious point, however, is that even when the primary growth appears to be in every relevant respect a carcinoma, the metastases become successively more sarcomatous in character, and the last crop of all is a pure sarcoma.

Extensive Thrombosis of the Central Vein: Recovery of Vision to practically normal.—EUGENE WOLFF, F.R.C.S.

Mrs. H. had, three years ago, what I thought was a complete thrombosis of the left central vein. Her vision was then less than $\frac{6}{60}$.

From the subsequent history I suppose this could not have been so, for her vision now is $\frac{6}{6}$ most. Her fundus now shows extensive new formation of capillaries on the disc (which makes its colour much redder than that on the other side) and pigmentation at the macula.

Thrombosis of Cilio-retinal Artery.—EUGENE WOLFF, F.R.C.S.

Harriet H., aged 68. Sight failed November 20, 1933, two days before visit. Right vision was then $\frac{6}{60}$. Right pupil reacted fairly well.

To the outer side of the disc there was a pale œdematous area (difficult to see) fringed with hæmorrhage. The break in the cilio-retinal vessel was visible.

25.11.33: Pale œdematous area now converted to the dense white of coagulation necrosis. Break in cilio-retinal vessel still visible.

2.12.33: Right vision less than $\frac{6}{60}$; pupil almost inactive. Fundus as above, but striate hæmorrhage in region of break in cilio-retinal vessel.

[*The report of other cases shown at this meeting will be published in the next issue of the* PROCEEDINGS *of the Section.*]

Section of Laryngology

President—MUSGRAVE WOODMAN, M.S.

[*December* 1, 1933]

DISCUSSION ON RECENT ADVANCES IN THE TREATMENT OF CARCINOMA OF THE ŒSOPHAGUS FROM THE SURGICAL AND RADIOLOGICAL ASPECTS

G. Grey Turner: The œsophagus is still the realm of experimental surgery, and though my first case of excision was carried out as long as twenty-five years ago, I am still undecided on many matters of technique.

For some years I have been expecting that in radium or in deep X-ray therapy remedies would be found that would displace radical operations from the realm of legitimate surgical endeavour. My own limited experience of these measures has been disappointing and the personal experience of my friends, both at home and abroad, has been equally so.

The surgical treatment of cancer of the œsophagus has always been hampered by the inaccessible situation of the part involved and by the almost universal idea that malignant disease of this organ is of a peculiarly virulent type and liable to disseminate at a very early stage. The examination of patients who have died of the malady certainly often discloses extensive local spread and involvement of the lymphatic glands with sometimes distant dissemination, but these cases have usually been unchecked by any form of treatment. Even in the worst cases there is probably a stage at which the disease remains localized for a time, and it is only during that stage that the condition may be amenable to radical treatment. In all probability malignant disease of the œsophagus is like similar disease in other situations, and that while perhaps one-third of the cases are unusually malignant, in the other two-thirds the baneful effects are for long a question of environment. It is a striking fact that in the five cases in which I have been able to complete the radical removal of the œsophagus there has been no evidence of dissemination.

The specimens of this condition in most museums show the disease very advanced and far beyond the hope of any radical treatment. In the College of Medicine in Newcastle, there is one specimen of a localized squamous carcinoma of the œsophagus without any dissemination whatever, which was found in a dissecting-room subject by Mr. James Whillis of the Anatomical Department. The man was 76 years of age and there was a history of dysphagia of four months' duration. Malignant disease of the œsophagus is not always rapidly fatal, and I have been much impressed by cases which have survived in comparative comfort for six months or more after gastrostomy, and in whom an ultimate necropsy has proved the true nature of the disease. In one notable case the patient lived for nineteen months after gastrostomy or twenty-one and a half months after the first symptoms of œsophageal

obstruction, and even then death was precipitated by perforation with a bougie. A long linear growth at the lower end showed only local spread.

In the past there has been little attempt to deal with these cases radically at an early stage. As a rule difficulty in swallowing has been allowed to drag on until it becomes, not only a great discomfort, but a serious menace to life. Thus valuable time is thrown away, and this is borne out by the clinical histories, for in many patients three to six months have elapsed between the first onset of symptoms and the stage at which some active treatment is seriously considered. In forty-six of my own cases this period was just under four months, and in many it was from six to nine months.

It should be remembered that the first symptom may be an attack of difficulty in swallowing which may pass off completely. This should be looked upon as a warning and an absolute indication for careful investigation. All surgeons ought to be familiar with the occasional yet outstanding successful results of radical surgery. I confess that I have always been fascinated by the story of Torek's patient, the old woman who had a growth removed by the transthoracic route and who lived comfortably with the aid of an external rubber œsophagus for nearly fourteen years and then died at a good old age from pneumonia. Lately my imagination has been stirred by the case reported by Arthur Evans in which the patient was alive and well twenty-three years after the removal of the pharynx and cervical œsophagus for cancer. It may of course be urged that these are rare and fortuitous happenings, but I contend that if we could overcome the technical difficulties and resort to radical surgery at an earlier stage they might be not infrequently repeated. I do not propose to deal in detail with malignant disease of the cervical œsophagus. I quite recognize that it presents many opportunities for surgical intervention and that the results of extirpation have been very encouraging, as in the series reported by Logan Turner. It seems to me, however, that the difficulties of restoration are very great, and that removal is often hampered by the desire of the surgeon to leave conditions favourable for repair. On the next occasion when I have to deal with this condition I propose to excise the growth freely without regard to repair of the defect and to make an upper œsophageal or pharyngeal fistula and at a later date attempt to construct an extrathoracic œsophagus. When the growth is low in the cervical œsophagus, or at the commencement of the thoracic œsophagus, some help in access may be gained by dividing the sternomastoid completely and resecting the inner third of the clavicle. With this aid the œsophagus can be separated and divided well down into the superior mediastinum. Many years ago I was impressed by the posterior mediastinal exposure when I had the privilege of assisting Rutherford Morison to remove a foreign body from this part of the œsophagus. The man was emaciated and it seemed to me to be a feasible method, but when I came to try this operation in the case of cancer I found it to be very difficult, largely for anatomical reasons. Arm-chair contemplation assisted by the alluring pictures in textbooks and surgical journals makes the operation appear comparatively simple, but a study of transverse sections of the thorax soon corrects any such impression. In any event, successful excision leaves the surgeon with the problem of restoration, and I am certain that local efforts at formation of a new gullet from skin flaps at the site of excision must give place to the construction of a new œsophagus by the anterior route. But in spite of what I have said the posterior exposure has one advantage that appeals to me, namely, that the surgeon has every opportunity of conducting the necessary manipulations under direct vision.

Years ago I was further attracted by a picture from Torek which showed a patient with the œsophagus enucleated from its thoracic bed and lying limp and dependent on the anterior chest wall. This suggested to me the idea that it might be possible to excise the whole œsophagus by enucleation, and led me to develop the operation which I have designated the " pull through " method, and which my friends compare

to the "drawing" of the medieval executioners. This plan has at last rewarded me with one complete success. I have also explored an œsophageal growth from the abdomen on eleven occasions in which I was not able to complete the removal. Briefly the steps of the operations are as follows: First operation.—Preliminary exploration of the abdomen to determine that there are no secondary deposits in the liver, or extension of the growth to the glands along the lesser curve. At the same time gastrostomy is carried out.

Second operation: Step A.—The abdomen is reopened through a middle line incision carried high up between the left costal margin and the xyphisternum. The left lobe of the liver is detached from the diaphragm and turned to the right, exposing the abdominal portion of the œsophagus. A quantity of one half per cent. novocain solution is then injected around the lower thoracic œsophagus to distend the cellular spaces around it, and in the hope of displacing the pleura. The peritoneum over the œsophagus is incised, and enucleation commenced by the fore-finger introduced through the hiatus and worked up as far as possible around the tube. When no further separation can be accomplished, the abdominal area is covered with sterile towels, and the field of operation is transferred to the neck.

Step B.—A transverse or oblique incision is made just above the left clavicle, dividing the sternomastoid. The cervical œsophagus is exposed by blunt dissection and separated by the finger as far down as the latter can reach. The œsophagus is then ligatured and divided as low down as feasible, but at least two inches above the growth. The lower end is carbolized or smeared with bipp and allowed to retract, while the upper end is brought out of the cervical incision where it is fixed to the skin without tension. The remainder of the incision is closed around it.

Step C.—A return is now made to the abdomen, and traction is made on the œsophagus. If it can be withdrawn from its bed well and good, but if not it must be dragged down while further separation is carried out by the fingers. Sometimes it has been necessary to introduce the whole hand into the posterior mediastinum to complete the separation. At this stage one or both vagus nerves will probably be divided or torn. When the œsophagus is freed from its bed it is ligatured at the cardia and cut away from the stomach, and the stump securely buried by purse-string sutures.

Step D.—The open œsophageal tunnel is closed by suturing the left lobe of the liver over its mouth, and the abdomen is closed.

This plan was carried out twice without meeting with success. In the first case the patient lived for a week, and in the second the man died suddenly on the night of the operation, and the post-mortem showed that both pleural cavities had been opened. The third was more fortunate, for the patient recovered, and it is this case which I want to bring to your notice this evening.

The patient was a man 58 years of age and one of the best type of north-country coal-miners, always cheerful and optimistic and an excellent patient. He first came under my observation at the beginning of April of this year (1933), complaining of serious difficulty in swallowing. This trouble had only commenced eight weeks before I saw him and had rapidly got worse. He complained that solids appeared to stick at the level of the lower end of the sternum and that he could only manage to swallow foods of the consistency of porridge and well-masticated bread. Under treatment from his own doctor he improved a little, but the disability was really progressive and during eight weeks he had lost no less than the three stones in weight. There were no external physical signs but the X-ray appearances (fig. 1) were characteristic of neoplasm in the middle of the œsophagus. On April 5, my surgical registrar made a gastrostomy and at the same time determined that there were no secondary deposits in the liver. As a result the patient improved, and I determined to make an attempt to remove the growth. There was no special preparation beyond the fact that the patient frequently swallowed small quantities of a solution of peroxide of hydrogen

of the strength of 1 in 10. On Friday April 28, I carried out the " pull through " operation. This was conducted under general anæsthesia, mostly by open ether, and this was entirely satisfactory. The general lines of the operation were as I have already outlined and have previously described in the Bigelow Lecture.[1]

When the finger was introduced through the hiatus by the side of the œsophagus the growth was felt just within reach but by pulling on the œsophagus and thrusting the finger up as far as possible I was able to separate it all round. Having done as much as I could from below, the operation field was then removed to the left side of the neck, the open abdomen being protected by sterile towels. With the finger gently thrust into the superior mediastinum the upper part of the growth could just be felt but I failed to reach the level of separation below. The œsophagus was then surrounded by a strong silk ligature at as low a point as it could be tied and this was

FIG. 1.—Skiagram showing constricting neoplasm in middle of œsophagus.
(Reprinted, by permission, from the *Lancet*.)

felt to be a little above the bronchus. It was cut across with the cautery, and the lower end and the parts around freely smeared with bipp. The proximal end which had been controlled by a light clamp was now brought out of the incision which was packed with gauze. Again, a return was made to the abdomen. It was found that the œsophagus was still firmly held near the root of the lung and that strong traction did not loosen it completely. Incidentally it was observed that this pulling did not appear to affect the patient adversely. As the œsophagus was drawn down towards the abdomen the left vagus was seen and divided with scissors. The right nerve was not seen and may have been spared, though on the other hand it may have been torn through in the final act of separation. As soon as the œsophagus was drawn into the abdomen there was a rush of air and it was found that a hole which would

[1] *New England Journ. Med.*, 1931, ccv 657, 674.

easily admit two fingers, had been torn into the right pleura. This was temporarily plugged with gauze. There was very little bleeding from the œsophageal tunnel. The fact that the right pleura was torn is of importance because I had contemplated collapsing the left lung as a preliminary, and had this been done the patient might not have left the table alive. The plugging of the rent in the pleura gave the anæsthetist an opportunity to stabilize the patient and after a short time normal breathing was resumed. When this stage arrived the œsophageal hiatus in the diaphragm was closed by suturing the left lobe of the liver over it like a lid, after the withdrawal of the gauze, and this effectually arrested the entrance of air into the mediastinum. The œsophagus was then ligatured and cut off from the cardiac end of the stomach and the stump invaginated by three purse-string sutures. The abdomen was then closed and a return made to the neck. The end of the cervical œsophagus was brought through

FIG. 2.—Showing comparatively localized growth in excised œsophagus.
(Reprinted, by permission, from the *Lancet*.)

a separate button-hole in the skin just below the inner end of the transverse incision and was anchored to the sternomastoid which was closed around it and the margins sutured to the skin, a No. 12 rubber catheter being tied into its lumen. The sternomastoid was repaired with catgut and the whole wound closed by interrupted sutures. The operation occupied one hour and forty minutes, the patient remained in good condition throughout and left the theatre remarkably well. The growth was a localized carcinoma of constricting type (fig. 2) and graded II by Broder's method. It had not extended beyond the wall of the œsophagus.

The after-progress was singularly smooth. The day after operation he was wonderfully well and did not admit of pain in the chest or any special discomfort. On the second day the pulse rose to 120 but the patient was looking quite well and expressed himself as comfortable. On the third day there was a troublesome

cough, but the pulse was slower and the patient obviously doing well. There had been a good discharge of saliva from the catheter in the cervical œsophagus, but on swallowing a little water some of it escaped by the side of the tube. A further ligature was applied around the œsophagus to refix the catheter in position and to prevent leakage, and the experiment was made of connecting the catheter with the gastrostomy tube, the patient then being able to swallow directly into the stomach. But for purposes of feeding the gastrostomy was used and it was generally found more convenient to allow the neck catheter to discharge into a bottle. At this stage swallowing hurt him a little and he preferred to spit out a good part of his saliva. Despite minor troubles the patient continued to make an excellent recovery and was able to leave the hospital on the twenty-third day following the operation. By this time he had been fitted with a rather larger catheter into the cervical fistula and this was followed by a rubber tracheotomy tube which was kept in position by tapes.

I have always felt that there could be little satisfaction in carrying this operation to a successful issue unless it was possible to restore the power of natural feeding. Fortunately many workers in various parts of the world have succeeded in constructing some type of new œsophagus which functions satisfactorily, and numerous methods have been employed. I would like to say that in my view the best method is the one which I always associate with the name of Rovsing,[1] who constructed a new œsophagus by making a tube from the skin over the front of the chest. In my case I completed the lower end by an isolated loop of jejunum with which the gap between the skin tube and the stomach was bridged. This seems to me an excellent plan, although there are details of great importance which must be observed if it is to be successful. In the case which I have just related I intended to endeavour to construct a new œsophagus, and the first stage of the plastic operation was carried out on June 28, that is just a day short of nine weeks after the date of the first operation. At this time he was in very good general condition, happy and cheerful, though he did not appear to have gained much weight. The first stage was the formation of a skin tube extending slightly obliquely from just below the clavicle to the costal margin, to the left of the sternum. This tube was made after the plan of Professor Rovsing, and with the help of the practical points mentioned by Mr. H. H. Sampson, of Birmingham, in his description of a recent case.[2] The suturing was done over a rubber tube the size of a No. 14 catheter, and the only difficulty was to provide a sufficient skin covering for the lower end, and to enable this to be carried out it was necessary to make two lateral tension incisions. A rubber tube was stitched into the cervical fistula to carry away the saliva from the operation area. At this stage I contemplated uniting the new tube to a cone of stomach at another sitting, after the method used by Rovsing, but on opening the abdomen I found it was difficult to get a sufficient cone, and though I fixed it into the parietal incision and just under the skin, it was not used. A week later the suture line was perfectly healthy, there was no sign of necrosis, and the patient's condition was good. On July 14, that is to say sixteen days after the first stage of the plastic operation, an attempt was made to connect the cervical fistula with the upper end of the skin tube. This was done by the same method employed for the making of the first tube, but to lessen the risk of contamination a rubber tube was fixed in the cervical fistula to act as a bridge between it and the skin tube. A week later when this wound was dressed it was found that the upper part of the area had broken down, exposing the end of the rubber tube which had slipped out of the cervical œsophagus. I feel sure this occurred as a result of the difficulty of bringing the rubber tube over the prominent clavicle. At first the defect was

[1] *Surg., Gyn. and Obst.*, 1926, xlii, 781.
[2] *Brit. Journ. Surg.*, 1933, xx, 447

comparatively small, but it soon gave way right down to the upper end of the original skin tube. It was decided to leave this alone until the lower end had been completed. Accordingly on July 8, the following operation was carried out: the abdomen was opened and the upper jejunum exposed, a loop about 8 in. long was selected opposite a primary arterial arcade. This was isolated from the remainder of the jejunum, the mesentery being carefully divided so as to avoid injuring the main vessels. Continuity of the intestine was restored by end-to-end anastomosis. I then proceeded to expose the posterior surface of the stomach about its middle, and one end of the isolated loop of jejunum was united to it by an end-to-side suture. Quite inadvertently it was the upper or proximal end of the isolated loop which was joined to the stomach. The other end of the loop of jejunum was temporarily closed by a running suture and brought through the lesser sac up in front of the stomach and out through the upper end of the abdominal incision. In this situation a bed was prepared for it by raising a little flap of skin and rectus sheath from the left side. The loop was then carried up to the end of the skin tube where it lay comfortably without the least tension. The end of the skin tube was then carefully isolated from its overlying dermal covering, and it and the intestine united. This part of the operation was done by joining the posterior surfaces with a series of mattress sutures of black silk, and this was followed by through and through sutures of continuous catgut. The latter was reinforced Lembert fashion by a series of silk sutures over the anterior aspect. The external skin was approximated over the suture line, great care being taken to evert the margins. In closing the abdominal incision one or two sutures were used to anchor the jejunal loop to the wound edges in order to provide for any drag on the anastomosis. The final result looked most satisfactory, and there was never any anxiety about the immediate after-progress. The man was more upset than by the previous stage of the plastic operation and indeed he seemed to feel this interference more than the removal of the œsophagus. For about a week he complained that he felt something sharp in his inside after feeding, and there was some little trouble in getting the bowel function restored. Even at this stage he said he felt some regurgitation up the skin tube, especially just after gastrostomy feeding. During the second week he seemed to get on fairly well, and when the wound was dressed there was no evidence of infection, but the skin looked bluish and the suture line indolent, and when the stitches were removed it was noticed that there was a little necrosis of the edges and that they were retracted a little. On the twelfth day I was struck by the appearance of the patient. He looked ill, was anæmic, and had a tendency to cyanosis, and evidently felt the cold, for though it was midsummer he had procured a pair of cotton gloves to keep his hands warm. The whole scars of the previous operations looked bluish, and it suddenly struck me that the appearance suggested a state of sub-nutrition associated with the onset of scurvy. On inquiry I found that the patient was having three pints of liquid nourishment per day at four-hourly intervals. The feeds consisted of milk, alternating with bovril, three eggs and about 6 oz. of whisky each day. He expressed himself as satisfied. On the next day he had a small secondary hæmorrhage from the upper part of the mid-line abdominal incision, the edges of which had also separated a little. On this day Dr. T. N. Armstrong was consulted about the diet. He took the same view as I did and advised that there should be more variety. The patient was accordingly put on vegetable soup, with invalid—instead of ordinary—bovril, and marmite, with in addition one teaspoonful of liver-extract cocktail before each feed. Dr. Armstrong also prescribed a mixture of arsenic and iron with some adexoline. From this time the patient made better progress, and the condition of the wound steadily improved, but in spite of this by August 28 a fistula had formed at the junction of the intestine and skin tube. The mucous membrane could be seen pouting through the opening which soon became about the size of a shilling. Occasionally after feeding there was

some regurgitation followed by escape of food. An attempt was made to deal with the fistula by carefully packing it with gauze in order to prevent the mucous membrane from separating the edges, and this certainly helped to diminish its size. The mid-line incision was considerably improved, and there were now quite exuberant granulations. On October 4 a further operation was carried out in order to unite the cervical fistula with the skin tube and to close the lower fistula. For the latter purpose the edges all round were under-cut. Some of the black silk sutures were found hanging loose and were removed, and this time the repair was completed by catgut throughout, care being taken to protect the suture line by everting the skin edges and drawing them together with mattress sutures.

The upper part of the œsophagus was then restored. This was done by making free incisions surrounding the gap, but in order to allow this part of the tube to lie comfortably without tension the clavicle and the cartilage of the first rib were exposed and a broad deep groove cut on the anterior surface thus forming a gutter in which the new tube lay very comfortably. In order to get sufficient skin-covering it was necessary to make two lateral tension incisions. After this interference the patient did well, and from the first could swallow his saliva. The operation was done on a Wednesday and on the Sunday he surreptitiously sucked a dozen grapes and swallowed the juice. Exactly a week after the operation he was seen to swallow the last part of his gastrostomy feed, which went down with the greatest of ease. After this all swallowing except of saliva was strictly interdicted. On the fourteenth day a small area of exposed mucous membrane was noted in the region of the fistula repair and through the opening there was a thin mucous discharge. It was a tiny hole which would just admit the end of a quill. On the seventeenth day after the operation the patient swallowed a pint of liquid food and there was very little leakage; the pouting mucous membrane in the fistula was cauterized. Three weeks after the operation the patient was very well and said he felt as if he might have been at his daughter's wedding; two days later he ate some wedding cake.

Six weeks after the last stage the gastrostomy tube was removed and the patient was able to take all food by the mouth. On this day a film (shown at the meeting) was made at tea-time when he had a poached egg with three slices of bread and butter, two pears and half a pint of tea. There was scarcely any leakage. Next day a small rubber patch was fixed over the fistula by McNeill Love's method. This was completely successful for forty-eight hours, when leakage restarted and the patch had to be removed. The fistula was now a good deal larger so that the gastrostomy tube was reinserted and a few days later the fistula was exposed and closed by suture. This time the whole area was covered by a flap of skin so that the suture line in the external skin and the deep sutures were not superimposed.

So far as the operation for the excision of the œsophagus is concerned, my failures have been the greatest possible encouragement and I want particularly to refer to the case of a man, aged 56, who lived for eight weeks after removal of the thoracic œsophagus together with the whole stomach and spleen (fig. 3) and whose death was due to failure of technique rather than to any inherent difficulty. He came under my care when in bad condition and as a first stage I explored the abdomen and carried out jejunostomy; five weeks later the major operation was performed. From the first I considered this patient an unsuitable subject because he was a nervous bulky man, with a deep chest, a short thick neck and shortness of breath from emphysema.

The operation was carried out as in the case I have already detailed, except that the great omentum was used as a plug to close the lower part of the œsophageal tunnel. In order to get the cervical œsophagus to come to the surface without tension I had to separate it rather freely towards the pharynx. Having got it to the surface I suspected that its blood supply was impoverished and matters were

made worse by introducing a large self-retaining catheter (No. 18) in the hope that we might effectually control the escape of saliva and keep the patient more comfortable. He got over the ordeal of the operation quite well and all appeared to be going on happily until the fourth day when there was an abundant escape of offensive fluid from the neck wound. The catheter was loose and had to be removed when it became clear that the œsophagus in the neck had sloughed and was partly retracted

FIG. 3.—The whole stomach and œsophagus together with the spleen removed for carcinoma.

so that its lumen was communicating freely with the posterior mediastinum. One would have expected that as a consequence of this calamity the patient would have succumbed almost at once to acute mediastinitis, but he lived for nearly eight weeks. During that time the œsophageal tunnel was irrigated two or three times a day from the wound in the neck, and at one time we had reason to hope that this tunnel was becoming obliterated, and that a fistula would form in the neck, leaving us only with

the problem of making a new œsophagus. To add to his troubles a portion of the great omentum prolapsed through the lower end of the abdominal incision. One can only say that this man slowly died from septic absorption because we were not able to shut off the œsophageal tunnel from the pharynx, nor did we succeed in draining it from a dependent spot. At the necropsy the lower part of the tunnel, which had been plugged by the omentum, was found to be safely obliterated and indeed the omentum had become so closely incorporated with the cellular tissue that it could not be separated without tearing. The upper part of the tunnel was really an abscess cavity but with smooth walls lined by fine granulations, and beautifully shut off from the surrounding parts without evidence of any extension of the septic process. Most of the œsophagus in the neck had disappeared and the lower end of the open pharynx communicated directly with the postcricoid space. But the most encouraging feature of all was the entire absence of dissemination of the growth.

In the last case in which I operated I must again confess failure due to technical errors, but errors which it ought to be possible to avoid in the future. The patient was a female, aged 57, who gave a history of dysphagia of four months' duration. Everything went well at the operation until in the concluding stage the pleura was torn. Even so the patient soon got over this accident and left the table in good condition. For the first four days progress was good but after that time she was obviously not so well and there was evidence of some profound nutritional change. From the first there had been a little leak by the side of the gastrostomy tube and about this time it was discovered that the whole thickness of the abdominal wall between the gastrostomy and the middle-line incision had sloughed as though its blood supply had been completely interrupted. The sloughing area was cut away and measures taken to repair the leak but in spite of our efforts she developed parotitis, wasted rapidly, and gradually died on the ninth day following the operation. The necropsy showed that the infection from the sloughing abdominal wall had extended throughout the wound and had crept down the track of a drainage tube which we had brought from the neighbourhood of the œsophageal hiatus and from there it had reached the left pleural cavity. But even in this case we had learnt our lesson so far as the cervical œsophagus was concerned for the neck wound was completely healed and the œsophagus was united to the surrounding tissues without any sign of necrosis and there was no infection of the deeper tissues of the neck. I feel sure that had it not been for the accidental infection round the gastrostomy this patient would have recovered.

As a result of my experience I would like to say that radical surgery seems to me to hold out some promise. It will be better not to attempt the repair of the œsophagus in situ, but, after recovery from the excision, to supply the defect by making a new œsophagus by the anterior route. For growths of the upper end I would suggest an excision with formation of a cervical fistula and completion by a new œsophagus. For the lower end I would adopt the plan I have outlined, but for the middle portion I am inclined to give further consideration to the posterior mediastinal, or the transthoracic route. We require more information as to the exact living anatomy of these growths than we have got in the past and for that purpose I look to the radiologists and those who make œsophagoscopic examinations as well as to the result of surgical exploration. Those who have always looked on the black side of the cancer problem will be inclined to nourish this hopeless attitude with regard to this particular matter. To those more optimistic I would like to add the encouragement of my experience. I cannot forget that when Sir Spencer Wells was doing his pioneer work on ovariotomy his mortality was so high that there were those who said he ought to be prosecuted, and yet we now know how safe a harbour he finally reached and how his pioneer work helped to lay the foundation of the success which abdominal surgery enjoys to day. Many may criticize the presentation

of the one successful case which I present to you this evening because it is so recent that we can have no assurance as to the ultimate freedom of the patient from recurrence. To them I can only say that the restoration of the capacity of normal feeding with some hope of freedom from recurrence has already proved an ample reward for the patient and his friends who had been led to believe that his condition was beyond all human aid. The contemplation of this aspect of the matter again reminds me of Sir Spencer Wells and of a visit I made some thirty-three years ago to the house which had been his home at Golders Green. Over the portal I was delighted to read these words "Do to-day's work to-day." That I have always believed to be an excellent motto for the investigator, for it is a mistake to allow doubt and fears for the future to interfere with the work in hand.

Carcinoma of the Œsophagus treated by Radiation

By F. J. CLEMINSON and J. P. MONKHOUSE

(From the Ferens Institute of Oto-Laryngology, Middlesex Hospital.)

THE material on which the following study is based consists of all the cases of carcinoma of the œsophagus treated in the Throat Department of the Middlesex Hospital during the years 1925-1932. The writers are greatly indebted to Mr. Somerville Hastings and Mr. C. P. Wilson for allowing their cases to be included. In all there are 89 cases, 79 in men and 10 in women. Postcricoid growths have been excluded. Preliminary bioscopy was carried out in 72 cases of which 70 proved to be squamous-celled and one a spheroidal-celled carcinoma, while one was a myeloma. This last case was reported by Gordon Scarff in the *Journal of Laryngology*, xliv, 324.

The accompanying diagram shows the site of the growths, the dots representing the level of the upper edge. The tumours are classified as upper, middle and lower, the deciding factor being whether the greater part lies in the first three, the last three or the intermediate four inches of the gullet. The figures are:—

Upper	...	male 6	...	female 0	...	total 6
Middle	...	male 50	...	female 5	...	total 55
Lower	...	male 23	...	female 5	...	total 28

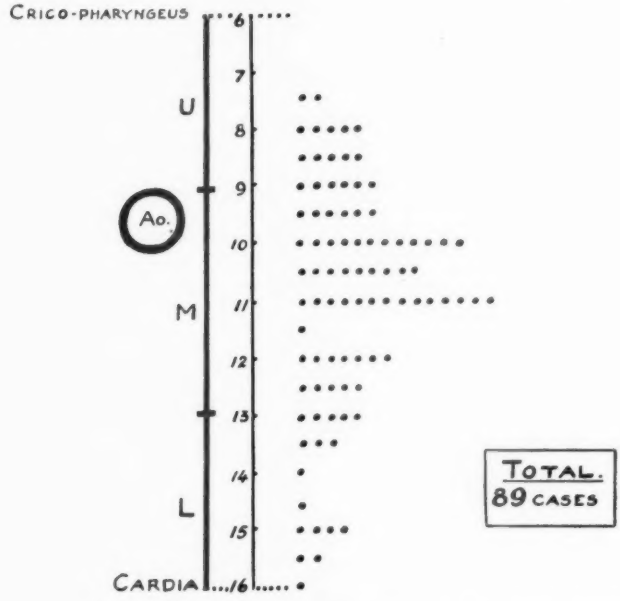
The general mode of treatment has been as follows: First an œsophagoscopy for diagnosis, with removal of a fragment of the growth for section. Next the patient is examined by X-rays to determine the length of the stricture—and for this examination the Trendelenburg position is essential; otherwise the lower end is undefined. From this information the dose of radon to be used and the length of the applicator are decided upon. Finally at a second œsophagoscopy the radon is placed in position and left for seven days.

In the earlier cases radium bromide was used, but later on radon took its place. The original applicators were Zeppelin-shaped containers made of silver and kept in place by a silver wire long enough to be passed round the head of the patient. The internal screen was of platinum 0·5 mm. thick. In 1929 acting on a suggestion made by A. J. Wright, radon seeds were used, applied by means of a Souttar's tube. A layer of strapping, sticky side out, is wound on the tube and to this the seeds are made to adhere in groups of four, secured still more firmly by a circular silk ligature round each group. Over all is applied a spiral band of thin dental rubber. A long silk thread is passed downwards through the lumen and brought back along the outside of the tube and through the collar. This does not interfere with the passage of the Souttar's tube through the œsophagoscope, prevents the radon from passing through the stricture

into the gut, and is finally used to withdraw the tube at the end of the exposure period. The average number of applications in our series has been 1·5 per patient.

In 1928-29 four cases were treated by thoracotomy. Following a preliminary collapse of one lung, the chest wall was opened and radon seeds were inserted into the periphery of the growth. This was a rather severe proceeding for old and debilitated patients and as it did not promise to lead to a marked prolongation of life it has not been pursued further. A report of these cases was read before this Section by one of us in 1930 and is published in the *Journal of Laryngology* (xliv, 577).

In a fair percentage of our cases the ulceration disappeared after treatment, either leaving a stricture with smooth walls or in a few cases leaving no sign at all,



SITUATION OF GROWTHS. EACH DOT REPRESENTS ONE CASE AND SHOWS THE UPPER LEVEL OF THE GROWTH.

both lining and mobility of wall being normal on inspection. Post-mortem microscopic examination of the gullet by section showed, however, that above and below the former site of the growth columns of cancer cells could be seen lying in the lymphatics between the muscle bundles, and in cases where a stricture persisted they could also be seen at the level of the actual site. This led to the trial of a modified tube with an extension of one inch above the shoulder, ending in a second collar to fit the end of the instrument used to push the tube into place and increased in length by another inch at its lower end, to allow for irradiation not only of the stricture itself but also for a distance of one inch above and below it. Thus for a stricture of say $3\frac{1}{2}$ in. the tube would be 6 in. long.

The seeds used till recently were screened with 0·3 mm. of platinum, but lately a thickness of 0·5 mm. has been substituted, which has entailed the use of Souttar's tubes with a narrower lumen so as to maintain the relative projection of the shoulder.

The general attitude has been to avoid gastrostomy if possible. It was found that up to the time of death the majority of the patients were able to swallow and a preliminary gastrostomy was only done for some special reason and was not found to lengthen life. But among the cases of the last eighteen months a small series of Mr. C. P. Wilson's seems to indicate the advisability of making gastrostomy a preliminary to all other treatment, especially if the operation be preceded by the total extraction of all remaining teeth.

Results.—Speaking generally it may be assumed that the moment at which patients seek advice in the out-patient department marks the attainment of a certain degree of urgency in their symptoms. This point is the beginning of what we have called their "survival period," which is ended by death, and the length of this time has been chosen as a fair estimate of the success of the treatment.

The average survival period for the whole series was 5·6 months (for growths in the upper part 6·7 months, in the middle part 5·4 months, and in the lower part 6·9 months). For the 10 women it was 8·5 and for the 79 males 5·2 months—a rather surprising result. The average length of the history of dysphagia was in females 5·4 and in males 3·8 months; that is to say, the females have both a longer history and a longer survival period. This relation of history to survival period is also somewhat surprising and suggests that a short history does not necessarily indicate that the case is "earlier" in the sense of being less advanced and so more amenable to treatment than one in which the history is longer. This suggestion is confirmed by a study of the survival times of patients grouped according to length of history, as shown in the following table (though the numbers are too small for any general conclusion).

History of dysphagia in months ...	1 to 3	3 to 6	6 to 9	9 to 12
No. of cases in each group	18	20	8	5
Average survival period in months ...	4·9	5·6	6·7	8·0

It would be interesting to discover whether the microscopical characters of the tumours can in any way be correlated with the differences shown in these groups.

If the series be divided into three chronologically arranged groups so that A contains the first 30 cases, B the next 30 and C the last 29 cases, the survival times are: A, 5·9 months; B, 5·7 months; C, 5·3 months. In other words, we have failed to secure prolongation of life by any modifications of method which have been made.

For the 10 cases in which a preliminary gastrostomy was carried out the over-all survival time was 5·5 months, but in Mr. Wilson's recent cases it was about twice this period.

In some of the most recent cases of one of the writers the dose of radon has been increased by about 50% above the usual one (which is 7·5 mc. per inch) and, if anything, these patients have lived for an even shorter period than the average. Perhaps the optimum dose is a moderate one of say 5 mc. to the inch (or 2 mc. per centimetre) screened by 0·5 mm. of platinum, and the most favourable interval between the application is probably from two to three months.

Deep X-ray therapy, inasmuch as each dose reaches the periphery of the growth in greater strength than the centre, may hold more promise for the future than the central application of radon. In this series only one case is included which was treated solely by X-rays, and his survival time was ten months. One or two other

patients were treated by both radon and deep X-rays, but the results were not striking.

It was possible to obtain a post-mortem examination in 28 cases, and the results are given here in tabular form :—

	Cases
Mediastinal perforation by the growth leading to	
1. Para-œsophageal (localized) abscess	2
2. Generalized mediastinitis	4
3. Abscess in lung	5
Tracheal perforation	3
Perforation of bronchus	2
Aortic perforation (death from hæmorrhage)	3
Ulceration of intercostal arteries (hæmatemesis) ...	1
Bronchopneumonia	4
Pneumonia	2
Involvement of cardia and stomach	2
Œdema of lungs, following mediastinitis	1
Hæmorrhage into intestine	1
Carcinoma of descending colon	1
Secondary deposits were found in	
1. Mediastinal glands	7
2. Cervical glands	2
3. Abdominal glands (general peritonitis in 1 case) ...	5
4. Pericardium (suppurative pericarditis in 1 case) ...	3
5. Heart	11
6. Lungs	3
7. Liver	9
8. Kidney	2
9. Suprarenal	1
10. Pancreas	1

These results of treatment are so disappointing that we are left wondering whether it is not actually harmful to treat these unfortunate people by the application of radon to the centre of the growth and whether they might not live longer if their only treatment were a preliminary removal of all teeth, followed by a gastrostomy. Clearly they do not seek advice until peripheral extension and early metastasis have made it impossible for the radiation to reach the outlying parts of the growth with destructive strength. Indeed, the suspicion arises that there may even be a certain danger of stimulation of the rate of growth at the periphery, and thus the end be hastened rather than delayed. The only sign of a "silver lining" is that the number of cases in the series is too small for the figures to have anything more than a suggestive value.

Walter M. Levitt.—Hitherto the results obtained in the treatment of carcinoma of the œsophagus by X-rays have been very bad, although in rare instances improvement has been recorded. Thus, Finzi treated a patient in 1923 with a very extensive œsophageal growth which completely disappeared, although the patient subsequently died of secondary deposits. I reported a case in 1930, in which a growth in the œsophagus was replaced by a smooth, apparently fibrous, stricture, and the patient lived for nearly two years, during most of which time he was in reasonably good health. Holfelder has recently recorded a case in which complete disappearance of a cancerous growth in the œsophagus resulted from X-ray treatment. The patient died from bronchopneumonia five months after treatment, and at autopsy no evidence of growth could be found.

Apart, however, from these occasional cases, it is true to say that the results of X-ray treatment of carcinoma of the œsophagus have been almost uniformly bad, and the most that could be hoped for was a temporary and moderate relief of obstruction.

These results of treatment of carcinoma of the œsophagus by X-rays have been all the more disappointing since the histological characters of these growths are such

as to suggest that they should be radio-sensitive. Thus, Broders and Vinson state that over 90% of all œsophageal growths belong to Grades III and IV of their histological classification. Moreover, post-mortem evidence has shown that metastasis is relatively uncommon in carcinoma of the œsophagus; 36% of 125 cases in Blaukwuip's series reported by Abel and 21% of 51 autopsies carried out at St. Bartholomew's Hospital reported by R. W. Raven, were free from any metastasis.

The problem of the treatment of carcinoma of the œsophagus is therefore in a large number of cases the problem of the treatment of the local disease, and this, as we have seen, is of a histological type which should prove radio-sensitive. On the assumption that the failure of the disease to respond to X-ray treatment, as hitherto applied, has been due to insufficient dosage reaching the growth, a technique has recently been worked out at St. Bartholomew's Hospital by means of which it has been possible to apply enormously increased doses to the œsophagus. Without entering into technical details, suffice it to say that the principle is the application of large daily doses of X-rays through multiple long narrow fields placed at intervals all round the chest wall. The fields have been made long—just under 7 inches on reaching the œsophagus—because of the known tendency of the disease to submucous spread up and down the gullet; and they have been made narrow so as to permit of the application of a large number of fields all accurately directed upon the œsophagus. As previously indicated, the treatment is carried out daily for a period of from five to six weeks.

In all, eight unselected cases have been treated by this method. All the cases had high degrees of obstruction; the diagnosis was confirmed by œsophagoscopy in six cases. Of these eight cases, treatment had to be abandoned in one because of the occurrence of symptoms of pulmonary disease; the patient has since died of bronchopneumonia. The remaining seven patients are alive and all are able to swallow.

I. W. Y., aged 56 (Mr. Bedford Russell).—*First seen*, 16.5.33, with history of progressive difficulty in swallowing, over a period of four months. Could swallow liquids only with difficulty. Much loss of weight. *Radiographic investigation* showed a stricture of the œsophagus due to a new growth which extended from the third to the eighth dorsal vertebræ. *Œsophagoscopy* showed a typical ulcerated carcinomatous growth. A fragment taken for section showed a squamous-celled carcinoma. *High-voltage X-ray therapy*, 16.5.33 to 18.6.33. By the end of the treatment, patient was swallowing fairly well. Swallowing improved steadily, and on 27.11.33, œsophagoscopy showed a normal œsophageal, mucous membrane, with an easily dilatable œsophageal wall, through which the œsophagoscope passed with ease.

Patient has recently been an in-patient at St. Bartholomew's Hospital under the care of Lord Horder, with a right-sided pleural effusion, but he has now returned to work again.

II. A. L., aged 40 (Mr. Bedford Russell).—*First seen*, 29.8.33, with a history of progressive difficulty in swallowing, regurgitation of food, and pain in the lower chest for two months. Could swallow only liquids. Had lost several pounds in weight. *Radiographic investigation* showed the appearances of a carcinomatous stricture in the middle and lower thirds of the œsophagus. *Œsophagoscopy* revealed a typical ulcerated growth of the œsophagus. A fragment taken for section suggested epithelioma, but was not conclusive. *High-voltage X-ray therapy*, 29.8.33 to 26.10.33. By the end of the treatment, swallowing was greatly improved, and the present skiagrams show an apparently normal œsophagus. Patient has gained over a stone in weight.

III. H. H., aged 60 (Professor Gask).—*First seen*, 4.10.33, with a history of sudden onset of difficulty in swallowing in August 1933, since when he had not been able to eat solid food. Attempts at swallowing were followed by pain in the chest and regurgitation. *Radiographic investigation* showed an irregular stricture at the level of the fifth dorsal vertebra extending for about 3 cm. *Œsophagoscopy* showed an irregular ulcerated growth.

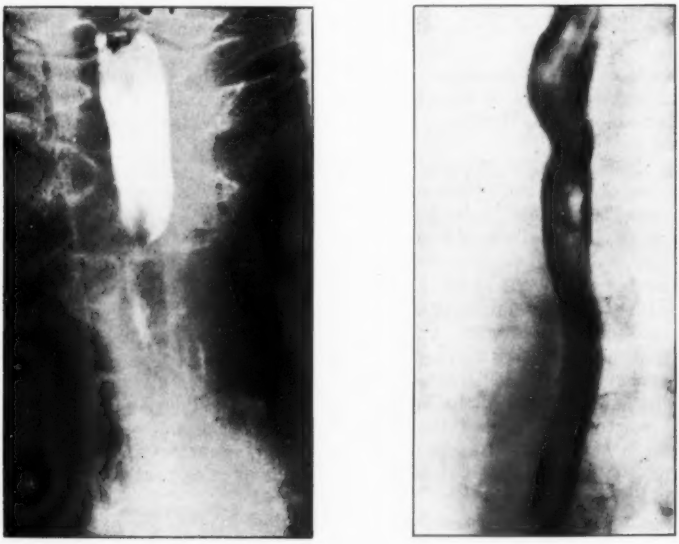


FIG. 1 (Case I).

20.4.33.—Before treatment. 24.11.33.—After treatment.

Note.—The skiagram on the left is a positive, that on the right a negative.

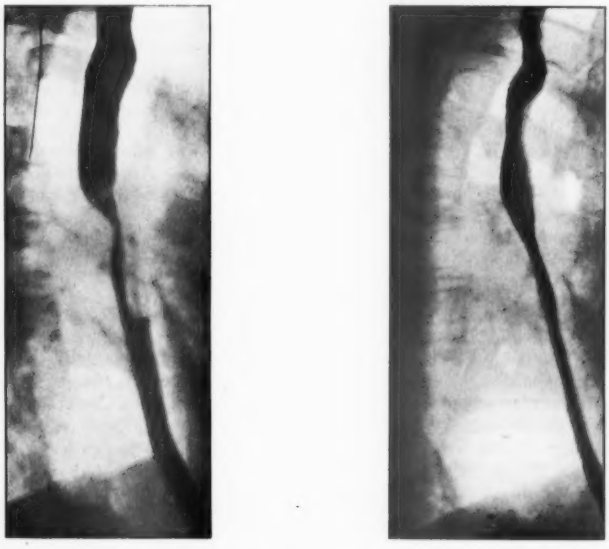


FIG. 2 (Case II).

21.7.33.—Before treatment. 20.11.33.—After treatment.

A fragment taken for section was not conclusive of the presence of carcinoma. *X-ray treatment* was begun on October 4, 1933, but had to be abandoned (because of progressive deterioration of patient's general condition, accompanied by cough and pyrexia), on October 26, after about half the treatment had been applied. Patient went steadily downhill and died on November 18. A post-mortem examination showed a hard non-ulcerated stricture of the œsophagus, with enlargement of the lymphatic glands around the bifurcation of the trachea. There was a right-sided empyema.

IV. A. G., aged 64 (Dr. Hinds Howell).—*First seen*, 28.9.33, with a history of gradually increasing difficulty in swallowing for six months. Could swallow only liquids, and swallowing was accompanied by substernal pain. Aphonia for five months. Had lost 2 stone in weight. *Radiograpic investigation* showed the appearances of a neoplasm at the level of the bifurcation of the trachea. The patient's general condition was very poor, and he

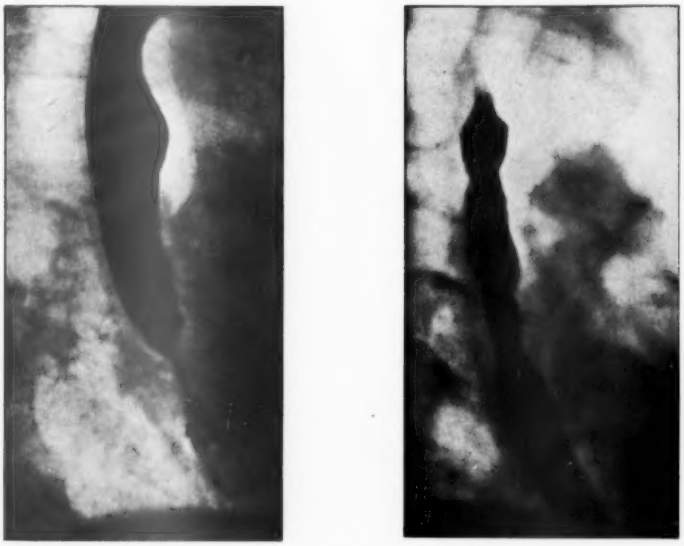


FIG. 3 (Case IV).
28.9.33.—Before treatment. 28.11.33.—After treatment.

was considered too ill for œsophagoscopy. *High-voltage X-ray therapy*, 28.9.33 to 30.10.33. Swallowing became, if anything, worse towards the end of the treatment, and gastrostomy had to be performed on October 31. Patient was then very ill, with a temperature of 101 to 102° F., with much cough and expectoration, the latter occasionally blood-stained. Swallowing gradually improved and the temperature returned to normal, and by November 21 patient was eating ordinary food, although there was still some cough and sputum. The improvement has steadily continued, and skiagrams taken on November 28 showed a free passage of barium through the œsophagus, with no evidence of growth, although distensibility of the œsophagus appeared to be impaired in the region of the previous stricture.

V. G. S., aged 52 (Mr. Ross).—*First seen*, 7.9.33, complaining of pain with a feeling of choking and regurgitation on swallowing, for two months. Pain had become persistent. *Radiographic investigation* showed the appearances of a carcinomatous stricture of the lower third of the œsophagus. *Œsophagoscopy* was not carried out. *High-voltage X-ray therapy*, 7.9.33 to 27.10.33. By the end of the treatment, swallowing was considerably improved. The skiagrams now show that barium passes freely through the œsophagus, the lumen dilating up well, but there is an irregularity at the site of the lowermost portion of the original growth which suggests the persistence of a remnant of active disease.

VI. R. H., aged 61 (Professor Gaskl).—*First seen*, 4.10.33, with a history of pain and difficulty in swallowing for two months. Could swallow fluids only. Much loss of weight. *Radiographic investigation* showed the appearances of a carcinomatous stricture of the œsophagus extending downwards from the level of the second costal cartilage. *Œsophagoscopy* showed an ulcerated œsophageal growth. A fragment removed for section was inconclusive of the presence of carcinoma. There was no doubt as to the clinical diagnosis. *High-voltage X-ray therapy*, 4.10.33 to 3.11.33. Pain on swallowing seemed to be increased during the treatment, but swallowing itself steadily improved after the second week. Patient can now swallow normally, and skiagrams show a free passage of barium down the œsophagus, which dilates well. There is no evidence of growth in the œsophagus.

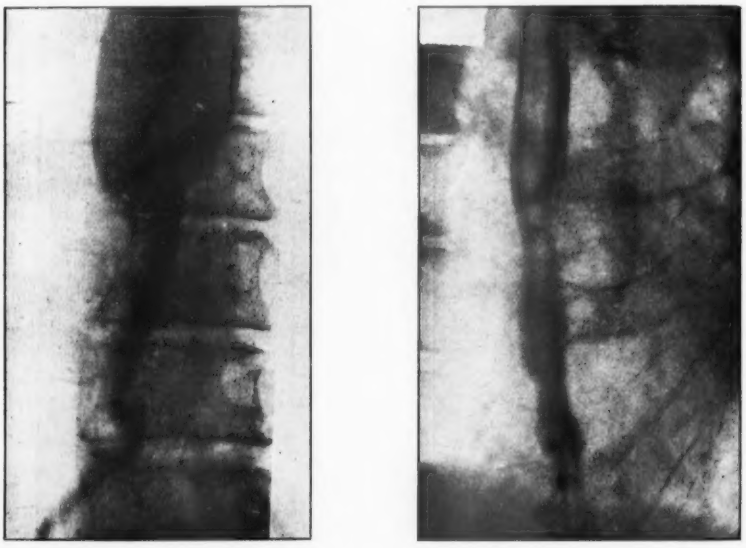


FIG. 4 (Case V).

29.8.33.—Before treatment. 20.11.33.—After treatment.

VII. F. B., aged 74 (Professor Gask).—*First seen*, 24.1.33, with a history of painful dysphagia for four months. *Radiographic investigation* showed the appearances of a carcinomatous stricture of the upper end of the œsophagus. *Œsophagoscopy* showed an ulcerated growth in this region. A fragment taken for section showed the presence of squamous-celled carcinoma. *X-ray therapy* (*by old method*), 24.1.33 to 13.11.33. Slight improvement followed treatment, but by June 1933 dysphagia was complete. Patient's general condition steadily deteriorated, until in September, the complete dysphagia was causing him such distress that it was decided to make a trial of the new method, although little hope was entertained for its success. *High-voltage X-ray therapy by the new method*, 14.9 33 to 24.10.33. By the end of the treatment patient was swallowing normally and continues to do so. Skiagrams taken after the treatment show a free passage of barium down the œsophagus, which dilates normally. Towards the end of the X-ray treatment, patient had an attack of acute retention of urine, due to an enlarged prostate. This necessitated a catheter being tied in ; this has been retained ever since. Although this patient is swallowing normally, his general condition has not improved, and the presence of secondary deposits is suspected.

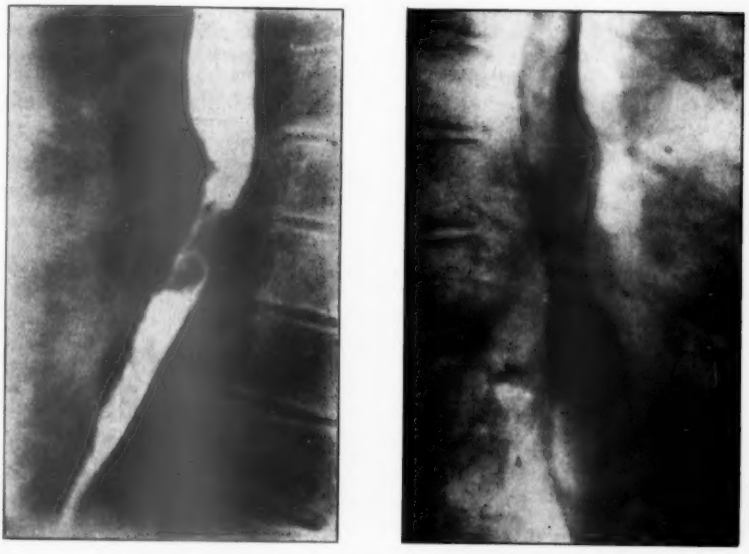


FIG. 5 (Case VI).

11.9.33.—Before treatment. 24.11.33.—After treatment.

Note.—Skiagram on left is a positive, that on right a negative.

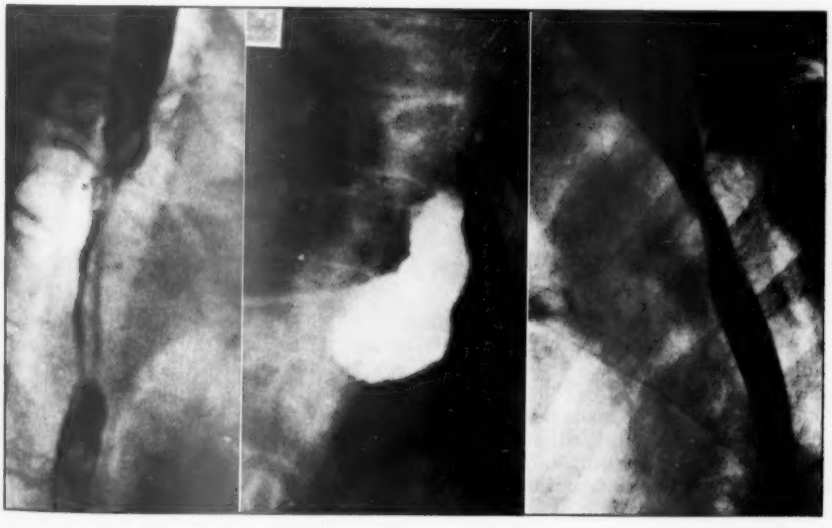


FIG. 6 (Case VII).

3.12.32.—Before treatment by old method. 14.9.33.—Before treatment by new method. 14.11.33.—After treatment by new method.

Note.—The skiagram in centre is a positive, the others are negatives.

VIII. R. M., aged 67 (Mr. Corbett).—*First seen*, 26.9.33, with a two months history of dysphagia which had been complete for one week. A gastrostomy had been performed a week previously. *Radiographic investigation* showed the appearances of a carcinomatous stricture extending from the level of the fourth to sixth dorsal vertebræ. *Œsophagoscopy*

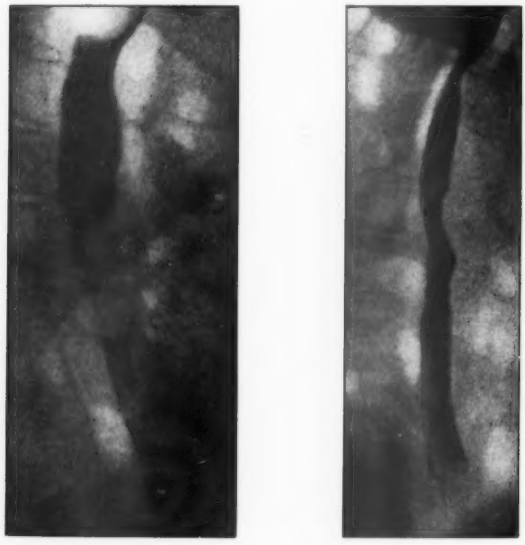


FIG. 7 (Case VIII).
10.8.33.—Before treatment. 20.11.33.—After treatment.

showed a friable bleeding growth. *High-voltage X-ray therapy*, 26.9.33 to 21.10.33. By the end of the treatment, patient was swallowing fairly well, and the swallowing has continued to improve. The skiagrams now show a free passage of barium down the œsophagus, which dilates well. There is no evidence of growth in the œsophagus.

[*Cases 1, 2, 5, 6, and 8 were exhibited.*]

It will be seen that in the seven cases in which treatment could be completed, the œsophageal obstruction has been relieved, and the patients can eat ordinary food. Radiographic investigation after the treatment has shown that thick barium paste is swallowed with ease, and the lumen dilates normally. No evidence of growth in the œsophagus can be made out in six, while in one, some irregularity can be made out at the site of the original stricture.

All the cases are recent, and in only one of them has sufficient time elapsed since the treatment to permit of the performance of œsophagoscopy. In the one case, however, œsophagoscopy has shown that the ulceration has completely healed, that the mucous membrane of the œsophagus at the site of the original growth is apparently normal, and that the œsophageal wall is sufficiently distensible to allow of the passage of the œsophagoscope.

This is what I have always believed should occur, if a carcinoma of the œsophagus could be cured by X-rays I have always urged that a so-called fibrous stricture following X-ray treatment alone of carcinoma of the œsophagus should always be regarded with the gravest suspicion. We do not see thick contracted scars after X-ray treatment alone in more than a very small proportion of our successful cases of carcinoma of the mouth and throat, and there would appear to be no reason why they should occur in the œsophagus.

It is obviously far too soon to draw any conclusion from such a recent series of cases. It is only to be expected that three or four of these cases already have secondary deposits, and in fact in two of them there are clinical grounds for suspecting that such deposits exist. It is clear, however, that as a result of X-ray treatment in a large proportion of cases of carcinoma of the œsophagus the growth can be made to disappear, or at least, so to diminish in size as to restore normal, or almost normal, œsophageal function. Anybody who has had an opportunity for observing the plight of these patients in the last stages of their disease, when they cannot even swallow their saliva, will agree that even for the sake of the primary result the X-ray treatment is worth while, and we may be permitted to hope that in at least one or two of the cases the result may be permanent.

All the cases referred to in this communication have been treated by large doses of very hard X-rays accurately concentrated upon the œsophagus. It is remarkable how little the patients felt the effects of their treatment. Two of them came up daily as out-patients throughout the whole course, and were comparatively fit at the end of it. In one case in the series, a certain amount of vesication occurred over a small area at the back of the chest. This gave rise to comparatively little discomfort and healed up completely in five days.

It cannot be too strongly emphasized that it is solely by the use of adequate doses of very hard rays such as are only produced by the best modern high-voltage apparatus that the best results can be obtained in malignant disease.

There is a school of radiotherapists in this country still urging the use of small, so-called stimulating, doses of soft rays in malignant disease, in spite of the fact that such methods have been abandoned for many years in all other important centres of radio-therapy in the world. It is claimed by the devotees of this school that heavy doses of hard rays are dangerous. That this is not necessarily so is demonstrated by the patients shown to-day. I would point out that although very large doses were applied to these patients, these doses were strictly localized to the œsophagus and its neighbourhood, and accordingly the total X-ray energy poured into the body may have actually been less than when the whole body is submitted to the so-called stimulating doses with a considerably lesser intensity. It is merely the application of the old method of small, short-distance cross-firing fields to the intensive split-dose technique which has been developed over a period of years at St. Bartholomew's Hospital.

I wish to acknowledge my indebtedness to those members of the staff of St. Bartholomew's Hospital (mentioned in the text) who have kindly provided the cases and beds.

[This work was carried out in the Radiotherapeutic Department at St. Bartholomew's Hospital, from a grant provided by the British Empire Cancer Campaign.]

The President said that Professor Grey Turner had referred to a case which was operated upon by Sampson; that was his (the speaker's) own case, that of a woman who had complete stricture of the œsophagus from end to end, owing to having swallowed a caustic fluid. He (Mr. Woodman) helped Mr. Sampson with the first operation, and it was easy to make a tube on the chest wall and an opening

into the stomach, but it was not so easy to connect the cervical œsophagus to the tube. The operator had a disaster when he was carrying out a trivial adjustment, and the patient died under the anæsthetic before the operation had been commenced. However easy these cases might be, relatively speaking, to the surgeon when the œsophagus could be left in the œsophageal tunnel—and it was comparatively easy to leave the œsophagus inside—it was a different matter to remove the œsophagus with the growth attached.

Professor Grey Turner had said that the radiologist was the best person to help him determine whether the growth was fixed, but he (the speaker) thought that the œsophagoscopist could accurately describe the appearance of the growth, how it moved and all about it.

He could confirm from his own experiments what Professor Grey Turner had said about the lymphatics of the œsophagus. After some trouble he had injected a specimen of œsophageal mucosa, and had been surprised at the fine reticulum of the lymphatics, especially when contrasted with those in a similar specimen from the stomach. The lymphatics of the gullet were too fine to admit carcinoma cells until they had burst through. That, he thought, accounted for the delay in dissemination and there could be no doubt that the spread was slow. Once begun, however, the extension was rapid.

With regard to fixity Professor Grey Turner had said that this part was like a bursa, and he (Mr. Woodman) could confirm that, from another point of view. He was experimenting on monkeys, and was trying to fix the œsophagus, which was always very mobile; he was at that time practising diathermy for the treatment of cancer of the œsophagus, and he thought that if he could stimulate reaction by round-celled infiltration round the œsophagus he would be able to destroy the growth safely. But he could not produce any reaction round the œsophagus. He passed the œsophagoscope on the monkeys and injected through the wall many kinds of irritating substances—such as iron, silica and coal-dust—and even passed electric needles through the wall, but in no case could he obtain an inflammatory reaction around the operation site. The œsophagus remained free and loose. That explained why it was possible to remove the œsophagus through the œsophageal tunnel.

He would have liked to hear Mr. Cleminson talk of approach to the œsophagus through the lateral wall of the thorax by the transpleural route. Mr. Barling and he (the speaker) had operated on a case in which radium transplantation by transpleural thoracotomy was carried out, but the patient died, probably from defective radium technique; hæmorrhage occurred on the tenth day.

Probably all members had had cases in which they had apparently removed the growth by the implantation of radon seeds, but the patient did not live; he suggested that the reason for that was that the growth was not attacked from the outside also. Radon seeds should be applied from the outside as well as the inside. Then there would be a crossfire of rays from the outer as well as the inner aspect.

Sir Thomas Dunhill said that he had approached these œsophageal growths transpleurally. Each operator should work in his own way, and those who were working by the same methods should group themselves together and help by co-operation, not by rivalry; he did not think that any special way could be said to be the only way. When he saw such cases as Dr. Levitt was able to show he was filled with hope. It was well known that radium could affect the growth and if the results were not perfect, it was probably because the technique had not yet been perfected. It should be borne in mind that in the beginning, œsophageal growths were local; they were confined first to the mucous membrane and the submucosa before they got beyond the musculature. If these growths could be removed at this

stage by the method of Professor Turner, it would give the patients their best chance of life.

The President had said that the approach to the œsophagus was not difficult. He (the speaker) had himself got down to it on a number of occasions, sometimes by transpleural means, sometimes behind the pleura, but he had never had a case in which he was able to free the growth completely from structures to which it had become attached. How to tell—before beginning the operation—whether that could be done he did not know. This could scarcely be determined by the radiologist; the bronchoscopist and œsophagoscopist could each help. In one of his cases the growth was fixed to the vertebral column, in another it was fixed to bronchi. None of his patients had been disturbed by the operation itself, though it was a lengthy one and the chest had been widely opened.

He therefore hoped that Professor Grey Turner would go on his way. His own view was that the transpleural approach did not add greatly to the gravity of the operation, and would add much to its safety. It might enable the organ to be freed at the proximal, and nicely finished off at the lower, extremity without adding materially to the danger.

G. Gordon-Taylor said he had little to add to what had already been said in the opening papers and by Sir Thomas Dunhill. In more than one case he had successfully extirpated a carcinoma of the cervical œsophagus on the lines of Mr. Wilfred Trotter's lateral pharyngotomy. He agreed with Professor Grey Turner's remarks about the anxiety concerning growths in the lower end of the œsophagus, in respect of the anastomosis between the lower end of the œsophagus and jejunum, duodenum, stomach, or whatever viscus was used, but he had had several successful cases. He had explored the thoracic œsophagus many times, in many ways, and at many sites, but invariably with disaster. The only occasion on which he nearly succeeded in a case of carcinoma of the thoracic œsophagus was when he employed the extrapleural method of Lilienthal.

N. S. Finzi said it was now more than twenty years since he had first shown a case of carcinoma of the œsophagus treated by radium at a meeting of this Section.[1] The patients at that date were treated by radium every six weeks, and one in particular was a man who tolerated the passage of the œsophagoscope very well. There had been a growth behind the sternum, and it had disappeared so completely after treatment that when the case was shown some members could not believe that a growth had existed. The patient lived another two years, and post mortem it was found that there was a spread of carcinoma along the œsophagus below the region where the original growth had been, while the part which had been treated had remained free from growth. In one case of the kind the patient had lived six years after treatment, subsequently dying from gastric ulcer, which she had had before the first application of radium.

In a case of Dr. De Santi, of Eastbourne, treated by X-rays ten years ago, the patient had the longest and largest œsophageal growth that he (the speaker) had ever seen. That patient had died a year after his original or initial treatment, and until the last he was able to swallow. Death was due to metastasis in the liver.

Another, a patient of Mr. Mollison, treated ten years ago, had a growth in the postcricoid region and upper part of the œsophagus; she was treated by X-rays on two occasions and was still alive and free from disease.

[1] *Proceedings*, 1911, iv (Sect. Laryng.), 153.

Laurence O'Shaughnessy said that the problem which interested him in these cases was the restoration of continuity after resection of the œsophagus. It was possible that the extraordinary results reached by X-ray therapy and radium for carcinoma might in time exclude surgery, but surgery would always be necessary for innocent tumours of the œsophagus. During six months abroad he had seen two such cases, in which surgical treatment had been very successful. The method that he himself used experimentally was not very new. He made an actual end-to-end anastomosis of the œsophagus instead of an œsophago-gastrostomy. So far as he had seen, the method was practicable for growths in the lower part of the œsophagus. He had seen a case of chronic peptic ulcer successfully operated upon and end-to-end anastomosis carried out.

Walter Howarth said that the possibility of carrying out local excision depended on the mobility of the œsophagus and the part in which the growth occurred, upper, middle or lower. The gullet was fixed behind important structures. At the upper end the only mobile portion of the œsophagus was below the cricoid, i.e. from there to the sternal notch. He had met with only two cases in that situation, the first of them in 1921. He had excised that section of gullet, and brought up the cut end from behind the sternum and united it to the deep pharynx. The patient lived for six years afterwards, He had a tight stenosis, therefore he could only swallow liquids and semi-solids.

The other case came to him nine years later, when he had seen more than a hundred cases of carcinoma of the œsophagus. He had hoped to show the man to-day, but he did not come. The growth was in the cervical œsophagus, but it extended so far down that he (the speaker) was unable to hook it into the wound, and so had to be content with putting radon seeds round it. That patient had remained cured of his growth for more than three years, and when examined a fortnight ago there was found to be stenosis, but it was a more supple scar than in the previous case, and he was able to swallow well. The other part of the gullet, which was fairly mobile, was that below the aortic arch and above the diaphragm, but he had yet to meet with a satisfactory case in that region. He had approached these by transpleural thoracotomy, which was not at all a difficult or severe operation. After producing collapse of lung a few days previously, it afforded a satisfactory approach, but made one realize what a short length of the gullet could be mobilized, if, however, a growth occurred in that region and the case was seen early, there would be no great difficulty in carrying out excision or applying radon seeds. What appeared, through the œsophagoscope, to be a small malignant ulcer, might be an enormous growth which was fixed all round to the aorta and bifurcation of the trachea. It was useless to put down radon seeds or radium or needles when the main mass of the growth was extra-œsophageal.

He had had dramatic instances of temporary cure by means of radon and radium, but he felt that intubation was as good a method, leaving out radon seeds round the tube, because carcinoma patients could be kept going for a long time with simple intubation. In one case which he treated with Souttar's tubes the patient had lived for eighteen months afterwards, and the tube was recovered, post mortem, having maintained the lumen of the gullet intact, while the whole mediastinum was a mass of cancer.

He was inclined to abandon the use of radium; he felt that simple intubation and the use of X-rays gave better results.

G. Ewart Martin said that attendance at this meeting enabled him to carry back to Edinburgh a ray of hope concerning the treatment of cancer of the œsophagus. For twelve years the subject had been worked at there, with only three

cases which could be looked upon as cures—apart from cases of cancer of the hypopharynx, which was more operable by the external approach. In Edinburgh a method used was suggested by Guisez, using tubes with the radium. They had tried in Edinburgh the direct implantation of radon seeds, also surrounding Souttar's tubes with radon and radium. But they had gone back to the Guisez method, as it seemed to be the simplest way to apply radium. He and his co-workers were not satisfied with radium in these cases, one reason being that though the local growth seemed to be cured, extension of it occurred, and the patient went downhill. Placing radium into the œsophagus destroyed its mucous lining, and checked the peristaltic movements, and the patient could not swallow. Hence these people, in many cases, had to have a gastrostomy made, and they led a miserable existence. He had had the opportunity during the past week of examining one man who had been treated three years ago with radium. The local growth had been cured, but 3 cm. above that was a second growth. At Edinburgh it was felt that deep X-ray therapy offered the best treatment.

T. B. Jobson wished to make a plea for a further trial of radon seeds around the growth inserted through the œsophagoscope. During the last twelve years various methods had been tried, such as Souttar's tubes and diathermy, and the lives of patients had been prolonged, but rarely was more than six months' further life vouchsafed to the patient. For the last two or three years his colleagues and himself had been using radon seeds, and had had one or two encouraging results. It was true that one swallow did not make a Spring, but one application of radon seeds might make a patient swallow. In January 1931, a man aged 62, came with a fungating mass in the œsophagus 11 inches from the incisor teeth; biopsy showed it was a squamous-celled carcinoma. In the following month ten radon seeds (1·5 mc.) were inserted as far as possible round the growth, and a skiagram showed them to be in good position. That man was now perfectly well, and swallowed ordinary food, and had gained weight. That was a great advance on a six months' prolongation of life by other and more drastic methods.

F. J. Cleminson (in reply to the President) explained that he had not dealt with thoracotomy in his paper, as he had done so elsewhere already. After that operation he had not found that the average survival period was longer than if nothing but endoscopic treatment had been carried out.

Carcinoma of Upper End of Œsophagus, apparently cured by the application of Radon Seeds.—WALTER HOWARTH.

Male, aged 65, was seen three and a half years ago with œsophageal obstruction; this was found to be due to carcinoma at the upper end of the œsophagus just below the cricoid. It was thought that it might be possible to excise this portion of the gullet, but, on exposing it from the outside, it was not possible to hook the lower end up into the wound, as it extended almost to the sternal notch. Ten radon seeds, 1 millicurie each, silver filter, were inserted into the growth. The patient has remained quite well since then, and the growth has become replaced by a fibrous stricture. This has been dilated upon two occasions.

Method of Implanting Radon Seeds in Œsophageal Carcinoma.—V. E. NEGUS.

The skiagrams [exhibited] show the seeds evenly distributed in the whole length of the growth. The method of insertion consists in measuring the length of the stricture with bougies, and placing the seeds by means of a straight introducer at different

levels. In most cases three seeds (1·8 millicurie, 0·5 mm. gold screenage) are placed in each cm. of the growth. If the growth is 4 or 5 cm. long, about twelve seeds are inserted.

Carcinoma of Œsophagus in a Man aged 45 treated with Radon Seeds. Patient free from symptoms two years later.—LIONEL COLLEDGE.

History.—Admitted to St. George's Hospital on April 16, 1931, complaining of difficulty in swallowing for four months and inability to swallow solid food for two months. Slight pain in chest. Had lost more than 2 st. in the previous four months. Voice had been husky for a similar period; cough not marked.

Examination and treatment.—The Wassermann reaction was negative. Report on barium skiagram: "A definite obstruction of the œsophagus in its lower third. The œsophagus above the site of obstruction is dilated, and below the obstruction the lumen is narrowed and irregular. The appearances are those of an organic obstruction, probably malignant." The right cord was fixed. The patient was œsophagoscoped under local anæsthesia on May 2, 1931, when an ulcerating growth with a raised edge was found at about the level of the fourth dorsal vertebra. Five radon seeds were inserted into the growth. On May 20, five more seeds were inserted and this procedure was again repeated on June 10.

Progress.—The patient was much improved and by the end of June 1931, was able to swallow solid food and had gained 10 lb. in weight. In March 1932, patient was free from symptoms, and on œsophagoscopy no evidence of neoplasm was seen. In March 1933, patient remains free from symptoms and has gained a further 8 lb. in weight. The right cord remains fixed.

Squamous Epithelioma of Posterior Pharyngeal Wall treated by Combined Diathermy and Radon Seeds.—E. H. RICHARDS.

Female, aged 51, seen eleven months ago with six months' complaint of discomfort in throat. Fixed and ulcerated cauliflower excrescence on posterior pharyngeal wall, in midline, $\frac{3}{4}$ in. wide, extending downwards $1\frac{1}{2}$ in. from level of soft palate. No palpable glands. Wassermann reaction negative. No history of alcohol or tobacco. Diathermy removal and implantation of radon seeds around and deep to growth—10 seeds of 2 millicuries each screened with 0·5 mm. of gold. Report on growth: "Exceedingly active though well-differentiated squamous-celled carcinoma of mucous type—the growth is encephaloid." No recurrence or glandular enlargement. Small suspicious nodule in midst of scar treated with diathermy needle two months ago.

Lingual Tumour: (Further Report of Case previously shown).—T. B. JOBSON.

The patient, a girl aged 16, shown at the meeting of the Section in May 1933, (*Proceedings*, 1933, xxvi, 1325, Sect. Laryng., 65) as a case of lingual goitre. She had a purple tumour at the base of the tongue just behind the foramen cæcum. The tumour was firm and was then about the size of a walnut. There were large veins radiating over it. As the girl had nearly died from spontaneous hæmorrhage from one of the superficial veins I decided to remove a portion by diathermy. A V-shaped central wedge was removed on October 7, 1933. Sections of this were reported by Dr. Nicholson to be malignant and probably epithelial.

On November 2, 1933, under evipan anæsthesia, 20 radon seeds were inserted round the tumour, which was then about twice the size it was in May. The tumour is now much smaller and the patient's voice is more distinct.

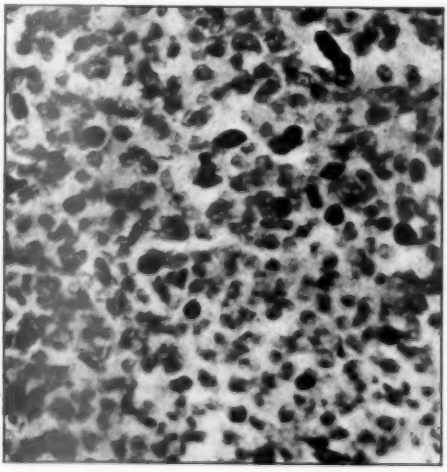
(*Pathologist's report* on further sections from growth at base of tongue.)

The tissue consists of a small wedge-shaped piece of material, with a thin border of epithelium from the tongue. The section marked X does show one or two small areas resembling thyroid tissue, but they are small and primitive. You will see small roundish areas staining a faint pink, very like colloid, and this is surrounded by a layer of flat epithelial cells. The whole thing, if it is thyroid, is very primitive, and the other sections on the second slide fail to show any of this thyroid element.

It is much more cellular, more vascular, with the cells showing pleomorphism, with, of course, a large amount of muscle tissue from the tongue. I had difficulty in coming to a conclusion as to the nature of the growth, and the fact that it had become larger recently (although there was a two years' history in all) made one suspect that it was in the nature of a myosarcoma. Professor Nicholson of Guy's Hospital kindly looked at it for me and he says that "the specimen shows fragments of new growth probably epithelial in origin and histologically malignant. There is nothing to say where it comes from, but I suspect that the enlargement is much more dangerous than a hyperplasia of puberty."—[R. C. MATSON.]

Melanotic Sarcoma of the Nose.—T. B. JOBSON.

Miss S., aged 73, had an operation for glaucoma some years ago. Recently she had nasal obstruction and was referred to me on November 9, 1933, by her doctor for removal of polypi. There was no nasal discharge and transillumination was



Melanotic sarcoma of the nose.

uniform and clear. The right nostril was blocked with "polypi." This mass was firmer than usual and of a dark blue colour. I removed a portion which bled rather freely. There is no evidence of disease in the orbit.

Pathologist's report (Dr. R. C. Matson).—"The sections from the tumour (see fig.) show a high degree of cellularity. The great majority of the cells are round cells, sarcomatous in nature, and these constitute the bulk of the tumour. A striking point is the number of more

or less round cells filled with melanin, and this pigment is not only confined to the cells, but has overflowed into the surrounding connective-tissue stroma.

It is a melanotic sarcoma, and for lack of evidence to the contrary, the pigment must be assumed to arise in the tumour itself."

Tracheotomy eleven years ago for Healed Laryngeal Tuberculosis, with Ankylosis of Cords: Further report on case previously shown.—ELEANOR LOWRY.

Female, aged 57. Shown at a meeting of this Section in March 1922, with the question of diagnosis. She had severe attacks of dyspnœa with inability to abduct the cords. The cords were thickened posteriorly. Tracheotomy was performed in April 1922. A piece of thickened tissue was removed from the right cord, and found to be not malignant.

She was found to have old pulmonary tuberculosis apparently healed and no tubercle bacilli could be found in the sputum. No dyspnœa since and the condition of the cords appears as in 1922.

Clinical Section

President—BERNARD MYERS, C.M.G., M.D.

[*December* 8, 1933]

Clinical and Pathological Aspects of the Adrenal Glands

By S. LEVY SIMPSON, M.D.

Dr. LEVY SIMPSON said that 75% of cases of Addison's disease were due to tuberculosis, 20% to atrophy, and 5% to other causes, e.g. syphilis, secondary neoplasm. Atrophy of the adrenal cortex might be associated with atrophy of the pancreas, leading to diabetes mellitus, or with atrophy of the thyroid, leading to myxœdema. Although a medullary lesion might play a part in the symptomatology of Addison's disease, the cortical lesion was the essential factor.

There were some fifty symptoms and signs of Addison's disease, many of which could be reproduced in animals by adrenalectomy :—

Wasting
Asthenia
Lethargy

Pigmentation
Desquamation

Anorexia
Aversion to fat
Nausea
Retching
Vomiting
Abdominal pain
Loin tenderness
Diarrhœa

Yawning
Stretching
Conjunctivitis
Photophobia
Hiccough

Low blood-pressure
Low blood-sugar

Achlorhydria
Secondary anæmia
Eosinophilia
Relative lymphocytosis
Pseudo-polycythæmia

Dehydration
Blood-urea +
Plasma volume −

Basal metabolic rate −
Subnormal temperature
Sensitivity to cold
Irregular pyrexia

Susceptibility to infection

Sensitivity to drugs
Sensitivity to toxins

Poor resistance to operation and shock

Retarded growth
Infantilism
Progeria

Psychological and emotional changes

Grimaces
Involuntary cries
Insomnia
Restlessness
Delirium
Coma

Scanty menstruation
Amenorrhœa
Loss of libido
Impotence

It had been stated that pigmentation, low blood-pressure and low blood-sugar had no counterpart in adrenalectomized animals, but this was no longer true if adrenalectomized animals were kept in a *chronic* state of insufficiency by inadequate doses of cortical extract. Wasting was a very important manifestation of adrenal insufficiency both in animals and man. Sun, friction, pressure and irritation, were accessory factors determining the site and depth of pigmentation. The latter might precede the general symptoms by some fifteen years, or in acute fatal cases might never be present. Similarly, in cases under treatment with cortin, where an acute crisis was actually precipitated by other factors, such as infection, death might occur before there was time for the pigment to appreciably increase. Cortin influenced both the dissolution and the deposition of pigment. In some cases there was a return to good health without a marked decrease in pigmentation. Aversion to fat might be associated with abnormal carbohydrate metabolism. Abdominal pain might simulate gastric ulcer, renal or gall-bladder disease ; if the pain radiated to the shoulder, it suggested diaphragmatic involvement. Loin tenderness was an important sign in tuberculous Addison's disease, and increased with exacerbations of

the pathological process. Diarrhœa was intermittent and often associated with long periods of constipation. Drastic purgatives were strongly contra-indicated and might precipitate a crisis. Yawning, stretching, conjunctivitis and hiccoughs constituted an important group of symptoms, often overlooked, but of diagnostic and prognostic significance; the latter two in particular were indications of insufficiency. The blood-pressure in Addison's disease might remain normal until the late stages, but was usually chronically low. It tended to vary with the general condition of the patient, with or without treatment. It was of interest to note that the blood-pressure tended to fall at the time of the menstrual period whether menstruation occurred or not; in crisis there was an additional acute fall, the latter (unlike the chronic low pressure) being due to diminution of blood-volume. Cortin might remedy this acute fall rapidly, within perhaps twenty-four hours, but the chronic low pressure did not tend to become normal for some weeks. In some cases the general condition became quite satisfactory without any appreciable rise of the blood-pressure. Observations about the blood-pressure also applied to a large extent to the blood-sugar, and variations of these two factors tended to be associated. Together with the low blood-sugar there was a diminution in hepatic and muscle glycogen, an apparent increased carbohydrate tolerance, and a hypersensitivity to insulin. Hypoglycæmic attacks might occur. The low blood-sugar had been held responsible for irritability, and inability to respond to extra effort.

The secondary anæmia was probably a sequel to achlorhydria, but both were not essential features of Addison's disease. The anæmia responded to iron therapy. It might be obscured by a diminution of blood-volume. Huth believed that the adrenal cortex was specifically concerned with the formation of red cells. Hyperplasia or tumour of the adrenal cortex might be associated with polycythæmia. The relative lymphocytosis was an important feature and was by no means necessarily associated with a secondary anæmia. The relative lymphocytosis that occurred in adrenalectomized animals might be corrected by cortin, and it had been suggested that agranulocytosis was dependent upon malfunction of the adrenal gland (Britton and Corey). Eosinophilia was probably associated with the pigmentation (Panton). Dehydration, concentration of the solid constituents of the blood, and a decrease in blood-volume, were very important features of the more severe phases of Addison's disease. The dehydrated appearance of the patient indicated an inability of the tissues to absorb water. Intraperitoneal saline injected into an adrenalectomized rat was not absorbed unless cortin was given at the same time. This was true of subcutaneous saline in Addisonian crisis. Also intravenous saline was not maintained in the circulation without the addition of cortin. The increase in blood urea seen in the subacute and acute phases was an expression of the decreased blood-volume, but terminally there was also a failure of renal function.

The basal metabolic rate was often normal, but subnormal in some cases, especially in crisis. A chronic subnormal temperature with periods of irregular pyrexia occurred in Addison's disease, and a marked sensitivity to cold was also a feature. The maintenance of temperature seemed to be an important function of the adrenal cortex, and cortin possessed the power of raising the temperature of hypophysectomized rats.

Treatment.

It was justifiable to compare the efficiency of cortin in Addison's disease with that of insulin in diabetes mellitus, but one must recognize the practical difficulties associated with the large doses necessary for adequate therapy. The cortical extract at present available was too weak for a convenient and easily applied form of therapy except in the less severe cases. The maintenance dose of cortical extract for different species was: rats $\frac{1}{2}$ to 1 c.c., dogs 1 to 2 c.c., cats 2 to 3 c.c., monkeys 6 to 12 c.c., and man 10 to 20 c.c. For repeated administration the intramuscular

or subcutaneous route was more convenient than the intravenous, and avoided the occasional occurrence of unpleasant reactions. Patients in crisis not infrequently had a rigor following intravenous salines and glucose administered with the usual precautions, and for this reason slow continuous intravenous salines and glucose by the drip method was preferable. If monkeys were allowed to remain in crisis for too long a period a condition of irreversibility developed, and this appeared to be true in man. Cortin did not appear to prevent the progress of the tuberculous or atrophic lesion, and it might therefore be necessary to increase the maintenance dose. Adequate doses, however, did appear to improve the function of the unaffected remnant of the gland, and permit in some cases a progressive decrease in the maintenance dose. Some patients were able to leave off cortical extract for some months or longer, and this suggested a temporary recovery of function or perhaps a storage of cortin. It indicated that intermittent therapy with large doses might be a reasonable proposition. As in diabetes, infection severely impaired the function of the remnant of the adrenal gland, and an immediate doubling of the maintenance dose was called for.

Accessory methods of treatment were: adrenalin by injection and by mouth, whole dried gland by mouth, Rogoff's extract by mouth, sodium chloride (Loeb), vitamin C, cotton seed oil, glucose, fluids, and tuberculin. The sodium chloride treatment of Loeb was based upon the finding of low blood-chloride values and increased chloride excretion in Addison's disease and in adrenalectomized animals. As regards the use of cortin in conditions other than Addison's disease, there was no convincing evidence of its value in myasthenia gravis, muscular dystrophies, most types of neurasthenia, essential hypotension, and hyperthyroidism. It was reasonable, however, to consider its use in certain cases of pregnancy, infection, post-infective debility, or the dehydration phases of chronic intestinal obstruction, severe operations (especially with previous malnutrition), pyloric obstruction, marasmus, diarrhœa and vomiting; also in hypocorticalism; including, perhaps, one variety of neurasthenia (Leyton).

The methods of assay of cortical extract were based on its effects in adrenalectomized animals, including maintenance of weight, power of muscular contraction, ability to do work, maintenance of temperature, rate of growth, increase in blood-sugar, and in hepatic glycogen, resistance to histamin and typhoid vaccine.

Although the cortex was the part of the adrenal gland essential to life, yet there was some indirect evidence that a pathological medulla played some part in the symptomatology of Addison's disease. When one remembered that adrenalin could influence blood-pressure, blood-sugar, basal metabolic rate, temperature, pigmentation, muscle tone, capillary tone and plasma volume, and that it was effective to some extent in Addison's disease and after adrenalectomy, it was difficult to ignore the potential results of an absence of adrenalin (or chemical precursor) in Addison's disease. Further evidence of a functional association between the cortex and medulla was the fact that the concentration of cortin was greatest in the zone of the cortex nearest the medulla (Harrop).

With the co-operation of Dr. G. Vilvandré it had been possible to demonstrate an interesting local action of adrenalin on the gastro-intestinal tract. If 1 to 2 drachms of 1 : 1,000 adrenalin were taken by mouth by a normal individual, pain was felt in the right epigastrium passing downwards and (a little later) below and to the left of the umbilicus. Radiological examination showed this to be associated with an active jejunal contraction. The pain might be preceded by a sensation of coolness in the corresponding areas. These preliminary experiments indicated why adrenalin by mouth (or whole suprarenal gland) might cause abdominal pain if the dose were too large. Although tremors and a constricting feeling in the chest, etc., sometimes followed large doses of adrenalin by mouth, a rise of blood-sugar did not occur and an appreciable rise of blood-pressure was exceptional both in normal man and in

Addison's disease. With the co-operation of Dr. C. E. Brunton the effect of adrenalin by stomach tube (1 to 4 c.c. of 1 : 1,000 solution) was tried in a spinal and in a decerebrate cat. No appreciable rise of blood-pressure resulted.

An interesting recent finding was the high concentration of vitamin C in the cortex; also it had been claimed that vitamin C decreased the pigmentation of Addison's disease. Cortical extract, however, did not contain vitamin C. Scurvy and pellagra might occur in Addison's disease, and Addison's disease might occur in chronic pellagra. Malnutrition resulted in hypertrophy of the adrenals, followed by congestion, hæmorrhage and atrophy. Cortical extract protected against deficiency of vitamins B and C, but not against deficiency of vitamin A (Lockwood and Hartman).

Adreno-genital syndrome.—The clinical manifestations of adrenal tumours were: pseudo-hermaphroditism (masculinization); homosexual precocity in both male and female and heterosexual precocity in the female; masculinization of the female and feminization of the male. In contrast, adrenalectomy and some cases of Addison's disease might show the following features: cessation of œstrus, abortion, absence of lactation, degeneration of testes, atrophy of seminal vesicles, and changes in the pituitary gland. Injections of cortical extract and cortical transplants were, however, disappointingly negative. Further, cortical extract did not repair the atrophy of sex organs following hypophysectomy; nor did it apparently influence the action of testicular extract or of prolan (Korenchevsky and Levy Simpson). It would seem that the secretion of the cells of a cortical tumour (or even of a cortical hyperplasia) was different in quality from that of a normal adrenal gland. Elliot (1914) had pointed out that the cells of the normal adrenal cortex were embryologically closely related to the sex glands. Krabbe (1921) had postulated that adrenal tumours arose from fœtal testicular cells which had been absorbed by the adrenal cortex in a phase of development. Geschickter (1933) observed such undifferentiated cells beneath the capsule of normal suprarenal glands. The fact that patients with virilism and tumour or hyperplasia of the adrenal cortex not infrequently suffered from symptoms of Addison's disease (weakness, pigmentation) suggested that the hyperplasia in these cases was not of those cells that normally secrete cortin. Leyton had recently suggested the need for a closer microscopic study of the adrenal gland. Broster and Vines (with the clinical collaboration of Gardiner Hill) had found that the adrenal cortex in cases of virilism, unlike the normal adrenal cortex, was stained deeply by Ponceau fuchsin dye. Another approach was the biological one, and in a case (B. C., p. 35) of masculinization of a female with enlarged clitoris (shown at the meeting) the urine appeared to contain a high content of the male comb-growth-stimulating hormone (Levy Simpson, Macbeth, Adler, de Fremery). If this preliminary observation were confirmed, it was of considerable significance and might differentiate certain types (or perhaps certain phases) of masculinization. Possibly also a chemical extract made from the adrenal gland of a patient with virilism would, unlike cortical extract, produce an effect on the gonads.

Cushing had made an invaluable contribution to the present subject by drawing attention to the occurrence of a basophilic adenoma in certain types of masculinization, etc. In these cases there was generally a hyperplasia of the adrenal glands, probably secondary. There was, however, no reason for believing that primary tumours of the adrenal glands did not occur and, if time permitted, did not lead to secondary changes in the anterior pituitary in the direction of basophilia. There was a good deal of clinical and experimental evidence showing a close relationship between the adrenal gland and the pituitary gland (anterior lobe); thus hypofunction of the latter resulted in many manifestations that occurred with hypofunction of the former, both clinically and experimentally: low blood-sugar, hypersensitivity to insulin, increased carbohydrate tolerance, low blood-pressure, subnormal temperature,

low basal metabolic rate, impaired sexual function, emaciation, asthenia. Hypophysectomy resulted in atrophy of the adrenal cortex, whereas adrenalectomy produced a diminution of the gonad-stimulating capacity of the pituitary, and certain microscopic changes. Extracts and grafts of the pituitary produced hyperplasia of the adrenal cortex. Some authors claimed to produce hypertrophy of the pituitary by cortical extract. In human pathology a basophilic adenoma of the pituitary had been found in association with: (1) hyperplasia; (2) adenoma; (3) carcinoma of the adrenal cortex. The changes in the adrenals might well be secondary, but it was very probable that primary carcinoma of the adrenal cortex occurred and resulted in an increase in the number of basophil cells of the pituitary gland. In some cases there might not be time for any secondary changes in the pituitary gland to occur. An apparently normal adrenal cortex had been described in association with a basophilic adenoma and Cushing's syndrome, but no special stain, such as Ponceau fuchsin, had been applied. The usual conception of the influence of the anterior pituitary gland on the homosexual glands was that of a stimulating one, but it would appear from a study of Cushing's syndrome that if the basophilic adenoma influenced the homosexual glands it was entirely an inhibitory influence. This seemed to be a very significant point. It might be that when the homosexual organs of an individual were inhibited, there was a spontaneous development of a heterosexual rudiment latent in all individuals. Looking through the case histories of Cushing's syndrome recorded in his book, there appeared to be no record of hypertrophy of the clitoris, or in the male of any mammary enlargement. Hypertrichosis could apparently occur with defective male sexual function such as delayed puberty in a male of 20. It was important to remember that Cushing's syndrome could occur in the absence of a basophilic adenoma, such as was seen in the male patient of Leyton, Turnbull and Bratton, and the female patient of Kepler (Mayo Clinic). In these cases the major lesion was a carcinoma of the thymus, and the thymus is an organ which is known to inhibit homosexual function.

Hypertrichosis in women occurred not only with adrenal tumours and pituitary basophilic adenomas, but also in more physiological circumstances such as pregnancy and after the menopause. In all these conditions there was hyperplasia of the adrenal cortex. Mild virilism in women was an extremely common condition and every phase could be found, from accepted normality up to obvious extreme virilism.

It was perhaps inadvisable to indulge in much arm-chair theorizing. The pituitary factor introduced by Cushing, and the new Ponceau fuchsin stain for the adrenal cortex introduced by Broster and Vines, were two new considerations with which the morbid anatomist would build up a more certain pathology in the future investigation of these cases. Further, there was a great field of activity for the biochemist, physiologist, experimental pathologist, and clinician, before the whole story of the adrenal glands and their relation to the anterior pituitary could be elucidated.

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(For extensive Bibliography see previous publications.)

Addison's Disease associated with Syphilis and Fracture of the First Lumbar Vertebra.—J. C. HEATHER, M.R.C.P. (Introduced by W. GORDON SEARS, M.D.)

W. D., male, aged 56, of English parentage, returned to England fifteen years ago, after living in S. Rhodesia for ten years. In hospital three years ago, with a compression fracture of first lumbar vertebra caused by a shutter falling on his back. According to the records there was then no pigmentation. Since accident has not been in good health and has complained of pain in back. Latterly has had shortness of breath, polyuria, loss of weight and increasing weakness. Bowels open thrice daily for last five months; motions looser than normal. No vomiting.

Admitted to hospital October 18, 1933, having collapsed in street.

On examination.—Fairly well nourished; intelligent but memory rather unreliable; tends to sleep for considerable periods of the day; generalized bronzing with scattered flecks of dark pigment, especially on arms and lower part of trunk; also patches on otherwise unduly pale buccal mucosa. Evening pyrexia up to 99·6 until eucortone treatment was begun.

Heart: No enlargement. Hæmic systolic bruit (now absent). Blood-pressure 110/60 to 126/64. Lungs and abdomen: No abnormality. Skiagram of chest: No abnormality. Nervous system: Pupils slightly irregular on contraction. Right ankle-jerk absent.

Skiagram of lumbar region.—Old compression deformity of first lumbar vertebra. No evidence of calcification of suprarenals.

Urine: Quantity 70 to 100 oz. in twenty-four hours. No abnormal constituents.

Blood-count: Marked secondary anæmia.

19.10.33: Hb. 30%; C.I. 0·35; R.B.C. 4,270,000; W.B.C. 8,000.

14.11.33: Hb. 75%; C.I. 0·55; R.B.C. 6,450,000.

Blood-sugar 95 mgm.%. Sugar tolerance normal.

Blood Wassermann reaction: Strongly positive.

Cerebrospinal fluid: Wassermann reaction, strongly positive; Pandy's test, positive; cells, 50 per c.mm.; gold curve 5555552200.

Treatment.—The pigmentation has diminished somewhat since intramuscular injections of suprarenal cortical extract (eucortone: ½ c.c. increased up to 5 c.c. daily) were started. Iron also given in large doses.

Adrenal Insufficiency.—G. M. WAUCHOPE, M.D.

Miss D. W., aged 33, comes of a healthy family; her father, mother, sister and three brothers are short, strong and inclined to stoutness. The patient is said to have been of similar build and constitution with a rosy complexion until December 1921, when she had an illness diagnosed as "gastric influenza" in which the symptoms were retching and extreme prostration; she never fully recovered and had a similar illness, ushered in by a fainting attack, in April 1925.

First seen July 1926, complaining of lack of strength and energy, anorexia, nausea, aching in right side and constipation. She had had amenorrhœa of three months' duration; the menstrual periods which had begun at the age of 14 were always scanty, at six weeks' intervals and associated with dysmenorrhœa. Since the illness of 1921 they had been more scanty and occurred at longer intervals.

Patient was small, thin, sallow, very slow in movements and in responding to questions; voice weak; could hardly walk. Skin dry, harsh, and yellowish; patch of brown pigmentation 4 inches square over right lower ribs where a mustard plaster had been applied three months before. Diffuse pigmentation on each cheek, and round nipples and umbilicus. No pigment on buccal mucous membrane. Heart-rate regular and slow (60 to 70 per minute). Temperature 96° F. Blood-pressure 98/60. Pupils widely dilated, hardly reacted to light. Knee-jerks exaggerated. Weight 5 st. 6¼ lb. (in 1920 it had been 9 st. 13 lb.). Sergeant's white-line test was positive. A test meal in August 1926 showed free acid 0. Total acid 14.

Progress 1926-1933.—General health much improved—patient is alert and more active. Pigmentation gradually disappeared. Menstruation: Occasional scanty periods until February 1931, since when amenorrhœa has been complete.

Digestion: Two attacks of vomiting 1928 and 1929, indigestion of the flatulent type has been decreasing; anorexia is less.

Weight has varied between 6 st. 1 lb. and 4 st. 13 lb. On the average is less now than in earlier years of period. In 1932 an attempt was made to increase the weight with insulin. Ten units were given each day for a fortnight with glucose, rest in bed and the application of ultra-violet rays. The attempt was a failure; the weight fell from 5 st. 2 lb. 4 oz. to 4 st. 13 lb.; the lowest point reached.

Blood-pressure has varied between 85/60 to 120/80; the usual systolic reading being 105-110.

The only serious relapse was in January 1928 when patient was limp, prostrated and yawning and blood-pressure was 85.

Various preparations of suprarenal extract have been given by mouth during the whole period—with occasional intermission of one or two months during which the blood-pressure has always fallen below 100. Examples of these preparations are: suprarenal tablets (Armour), gr. 2; ephedrine tablets, 1; suprarenal tablets (Parke Davis); solutions of adrenalin hydrochlorides; suprarenal whole gland tablet and also liquid (oxoid). This last has been the most successful and has been used now since October 1928. It has never been practicable to give larger doses, or to give adrenalin by injection.

Ovarian preparations were given in combination with suprarenal up to October, 1928. Hormotone; corpus luteum (Armour); ovarian residue (Parke Davis). Thyroid (fresh) gr. ½ has been taken since October 1928.

Illnesses: acute pharyngitis and tonsillitis in 1928, 1929 and 1933.

Present condition (29.11.33): Patient has almost lost the yellow colour though the skin of the abdomen is dusky. Pupils equal, moderately dilated, react to light and accommodation. Knee-jerks brisk and equal; heart regular, 62; blood 105/80; weight 4 st. 13 lb. ¼ oz.

She is alert and responsive but easily tired and depressed. She has always complained of swaying and a "sinking" feeling when walking, and still does so.

Dr. LEVY SIMPSON said that some points in favour of the diagnosis of adrenal insufficiency were: Loss of weight, lack of strength, anorexia, nausea, aching in the right side, amenorrhœa, hypotension, pigmentation, achlorhydria, yawning. Hypofunction of the adrenal gland and (or) of the anterior pituitary gland are possible causes of wasting of obscure origin. In mild cases unusual pigmentation only occurred if an irritant were applied to the skin, such as a mustard plaster as in Miss Wauchope's patient, or iodine in one of Dr. Levy Simpson's patient's. It was not uncommon for signs and symptoms of adrenal insufficiency to be negligible until intensified by the effects of an infection (as also occurred with mild diabetes mellitus). Also an infection such as influenza might cause a temporary hypofunction of a normal adrenal gland, or might be the starting point of an atrophy leading to obvious Addison's disease. The therapeutic test (cortical extract) was of diagnostic value in an indefinite case.

Addison's Disease.—S. LEVY SIMPSON, M.D.

M. S., a married woman, aged 54. This was the first case of Addison's disease to be treated by cortical extract in this country. The patient was demonstrated before the Royal Society of Medicine in December 1930 (*Proceedings*, 1931, xxiv, 497, Clin. Sect.), and before the Centenary Meeting of the British Medical Association in 1932 (*Brit. Med. Journ.*, 1932 (ii), 625).

History.—In 1917, following pregnancy, generalized pigmentation was first noticed, and this persisted. From 1925 to 1930 there were occasional attacks of vomiting. From May to November 1930, there ensued increasing weakness, asthenia, anorexia, nausea, retching, vomiting, pigmentation and occasional diarrhœa.

In November 1930, the patient was taken to a nursing home and a "crisis" developed. She was collapsed and semi-comatose; blood-pressure 86/65; subnormal temperature (97° F.). Her life was despaired of by the medical attendants and her condition was too critical for removal to the London Hospital, thirty miles away. Treatment consisted of 6 c.c. of concentrated cortical extract (prepared personally by Swingle and Pfiffner at Princeton) twice a day, intravenously, for four days (November 12 to 15). Patient made a dramatic recovery and was feeling well on the fourth day. (For details see previous reports.)

During the next few months dried extract was given by mouth intermittently and adrenalin was occasionally injected, but subsequently no treatment whatever was given.

Blood-pressure.—December 12, 100/74; February 1931, 108/80; March, 110/82. There was a slight temporary relapse in March, the blood-pressure falling to 100/78, and conjunctivitis occurring. Dried suprarenal gland given by mouth for a few days appeared to be beneficial. In April 1931, the blood-pressure was 120/80, and during the subsequent six months Dr. Stratford Collins reported variations of systolic blood-pressure between 120 and 90, observing that the blood-pressure tended to fall when menstruation was due, and that the condition of the patient was not so good at these times. In January 1932, Dr. Collins reported that she had gained 2 st. in weight, and was in excellent health. The pigmentation persisted. Menstruation was irregular in time and amount.

Patient has since been in good health. In November 1933, the blood urea was 30 mgm.%, and the blood-sugar 0·075%.

ADDENDUM.—The patient was again seen by the exhibitor on the day of the meeting. She stated that she was in good health and did her own housework. Menstruation ceased one year ago. On examination, the pigmentation was seen to be quite well marked and of characteristic distribution, including patches on the inner aspect of the lips and cheeks; the blood-pressure was 105 mm. systolic, 70 diastolic, the temperature was subnormal 97·2° F., and the pulse 78.

The question of the previous pregnancies was raised. Although permanent pigmentation dated from the 1917 pregnancy, marked temporary pigmentation was present throughout the previous 1909 pregnancy, during which the patient lost much weight and was troubled by chronic vomiting.

Addison's Disease: Abdominal Operation.—S. LEVY SIMPSON, M.D., and R. ALAN BREWS, F.R.C.S.

A. C., female, aged 39, unmarried.

History.—Patient was quite well until December 1931, when she began to have "fainting attacks." Apparently she fainted twice in the street, and was unconscious for about thirty minutes on each occasion. Early in 1932: Giddiness, weakness, loss of appetite, intermittent diarrhœa, insomnia and loss of weight; fainting attacks continued. Her doctor diagnosed "anæmia" and prescribed iron. Menstruation had become scanty. No previous illnesses of importance, but strong family history of tuberculosis.

April 1932: Seen at the National Heart Hospital by Dr. Janet Aitken, who diagnosed Addison's disease and secured patient's admittance to the Elizabeth Garrett Anderson Hospital. Some generalized pigmentation observed at that time. Radial and brachial arteries not palpable but oscillations of mercury manometer could be detected at 80 mm. Blood-pressure in the legs was 126 mm. Systolic murmur over præcordium; few fine râles heard at left apex. A mass was felt in the hypogastrium and thought by Miss Mocatta to be a uterine fibroid. Blood-count: R.B.C. 4,825,000; Hb. 52%; C.I. 0·54; W.B.C. 5,000. *Differential*: Polys. 56%; lymphos. 39%; hyals. 4%; eosinos. 1%. Adrenalin, by mouth and hypodermically, produced a slight improvement and some diminution in pigmentation.

Subsequently, 1 c.c. of eucortone given intravenously every day, with some benefit. During next few months patient received intermittent adrenalin therapy but increasing weakness and other symptoms caused anxiety.

February 1933: Dr. Aitken kindly discussed the case with one of us (S. L. S.) and sent patient for examination and treatment. Condition was as previously described. Pigmentation was characteristic of Addison's disease, but involved buccal mucous membrane only at angles of mouth. Blood-pressure in arm could not be ascertained; that in legs was 95 mm. History of recurrent hiccoughs elicited, this symptom being quite an early one. Patient developed a severe cold; family doctor reported anorexia, nausea and weakness. Eucortone, 5 c.c. daily intramuscularly at home with benefit. Patient admitted to the London Hospital three weeks later (under Dr. Robert Hutchison) apparently in excellent health. Blood-pressure (leg) 125. As brachial and radial arteries were still not palpable, an anatomical abnormality was diagnosed. Radiographical examination showed no evidence of cervical ribs or of calcification in region of suprarenal glands. Calcified glands could be seen, radiographically in the neck. *Chest*: No gross abnormality, clinically or radiographically, but a few small specks of calcification in both upper lobes (G. Vilvandré). Mantoux test (Dr. G. T. Western) positive. Fractional test-meal showed achlorhydria, and low total acidity. Fasting blood-sugar 0·077%: forty-five minutes after 50 grm. of glucose, 0·12%; two hours after the glucose, 0·166%. A specimen of urine taken at the time reduced Fehling's solution in equal volume, suggesting a low renal threshold. The blood urea was 0·03%. *Blood-count*: R.B.C. 5,000,000; Hb. 70%; C.I. 0·7; W.B.C. 3,600. *Differential*: Polys. 44·5%; eosinos. 6·5%; lymphos. 18%; large lymphos. 5%; large hyals. 6%.

Eucortone injections were discontinued on patient's admission to hospital and patient was observed. She remained perfectly well for seven days; symptoms of insufficiency then began to appear. At this period Dr. Rogoff had kindly sent some cortical extract ("interrenalin") which he had found of value, when taken by mouth, in Addison's disease. On the thirteenth day after admission patient was given this extract in half-ounce doses three times a day after meals. Definite and considerable improvement followed, and she left hospital on this extract in good condition. Attempts were made to prepare this extract in England but different batches of material showed variations, especially in the adrenalin content. At some periods each dose was followed by trembling, shakiness, pallor, tightness across chest, nausea and vomiting. Nevertheless, patient remained reasonably well, and menstruation, which had become normal under eucortone therapy, continued so.

During the past year, however, intermittent attacks of severe abdominal colicky pain had occurred and in consultation their relation to uterine fibroid was considered and operation was decided upon. It was recognized that patients with Addison's disease usually succumbed even under minor operations, but with the free administration of cortical extract we considered that the patient in this case could be tided over the operation. To control the course of events the extract by mouth was stopped and eucortone, 5 c.c. daily, was injected intramuscularly for two weeks previous to operation.

July 20, 1933: Admitted to the London Hospital under one of us (R. A. B.) *Blood-count* (July 26): R.B.C. 5,100,000; Hb. 60%; C.I. 0·6; W.B.C. 4,200. *Differential*: Polys. 28%; eosinos. 2%; lymphos. 57%; large lymphos. 12%; basos. 1%. Eucortone (5 c.c.) given daily until day of operation (July 27); on that morning at 8 a.m. 10 c.c. were given. Operation lasted from 10 to 10.40 a.m. Nembutal, 3 gr. by mouth, was given half an hour before operation. Anæsthetic (Dr. Gillespie): nitrous oxide and oxygen, with addition of a little ether when necessary. Subtotal hysterectomy (R. A. B.). Pathological report: Fibromyomata of uterus. Eucortone 10 c.c. intramuscularly given after operation and on subsequent days.

At no time did the patient's post-operative condition give rise to any anxiety; in

fact the ward Sister considered that it was better than that of normal patients who had undergone the same operation. Dose of eucortone reduced to 5 c.c. on July 1. Patient left hospital August 23. When next seen (September 22), she appeared to be in good health, but complained of occasional pains in left costal margin and loin; tenderness on palpation in latter region.

November 1: In excellent condition, feeling strong, and doing a good deal of house work.

In the evening of November 2, she retired to bed with "rumblings in the stomach," and hiccoughs. Sudden severe pain felt in left loin, persisting for two hours, during which period patient "dared not move or breathe." Respirations were cut short by the pain and were shallow and rapid. In the next hour or so there was a great desire to yawn but pain in side prevented this. Patient felt very tired during the next few days; aching and tenderness persisted in left loin, skin over this region being very sensitive. She was also troubled by a feeling of coldness, "as if my body gets colder and colder even in a warm room." Attacks of conjunctivitis also occurred. When seen November 13, her condition had improved but there was marked tenderness in the left loin. The patient complained of stumbling at times. Loss of postural sensibility and vibratory sense in legs (Wassermann reaction negative). Dose of cortical extract increased to 6 c.c. daily; dried extract by mouth also prescribed. The condition improved and the patient now feels quite well. Since the operation there has been no return of the lower abdominal pain, which appears to have been associated with the fibroids. From March 1933 up to date the patient has been receiving a course of tuberculin injections from Dr. G. T. Western.

Addison's Disease and Tetany.—S. LEVY SIMPSON, M.D. and Dr. C. GORDON-WILSON, M.D.

M. W., a married woman, aged 31.

History.—In 1923 she gave birth to her only child, and since then has been easily fatigued. In 1925 enlarged glands noted in right side of neck, and patient came to the London Hospital. Mr. W. S. Perrin excised one of the glands, and the pathological report was "caseous tuberculosis." Patient transferred to Dr. G. T. Western for tuberculin injections, which have been given up to the present time. From 1931 to 1933, loss of 12 lb. in weight. January 1933: Increasing weakness and pigmentation noted. April 1933: Dr. Western transferred patient to Dr. R. A. Rowlands' Out-patients' Department as a possible case of Addison's disease. May 1933: Admitted as an in-patient under Dr. Robert Hutchison. *Further points in the history*: Scanty and infrequent menstruation over a period of three months; anorexia, nausea, yawning for three weeks. An unusual feature was growth of hair on upper lip during three months previous to admission.

The family history is important, two sisters having died from tuberculosis (? meningitis) in early childhood.

On examination.—Patient appeared to be fairly well nourished, although her weight was only 6 st. 11 lb. The generalized pigmentation of the skin was quite characteristic of Addison's disease; a few small patches of pigmentation were present inside the cheek. Small discrete glands felt in right posterior triangle of neck. Blood-pressure, on admission, 140/90, but varied during next few weeks at hospital, lowest record being 100/70. Temperature was subnormal for several days at a time, but periods of irregular pyrexia occurred up to 101° F. Pulse 60-80; respirations, 24. Blood-count: R.B.C. 4,500,000; Hb. 75%; C.I. 0.83; W.B.C. 10,200. *Differential:* Polys. 54%; eosinos. 1%; lymphos. 35%; large lymphos. 4%; large hyals. 6%. Fasting blood-sugar estimates taken on various occasions: 0·09%, 1·1%, 0·074%, 0·079%; carbohydrate tolerance normal.

Blood urea 0·028%. Urine normal, except for an occasional haze of albumin. Wassermann reaction negative. Radiological examinations of the chest and adrenal areas were negative. Test-meal showed no free hydrochloric acid in resting-juice,

but a high level of 0·2% after 90 minutes; the total acidity closely followed the free hydrochloric acid.

Treatment with eucortone was begun May 17, with daily intramuscular injections of 2 c.c. On May 24, no improvement having been noted, the dose was increased to 5 c.c. daily. By June 10 improvement had begun, but as it was slow, the dose of eucortone was increased to 10 c.c. daily. Dosage kept at this level until July 5, then reduced to 5 c.c. daily. Patient was discharged from hospital on July 11, her condition being much improved. Pigmentation had almost disappeared, nausea had ceased; appetite had returned, lassitude had given way to a feeling of energy; the yawning stopped, and the weight had increased by 4 lb. Menstruation returned to normal while in hospital.

June 14, while in hospital under treatment with eucortone, patient had an attack of tetany, the clinical manifestations of which were unmistakable. At 9 a.m. she complained of stiffness of hands, and numbness and tingling of fingers. At 11.30 a.m. she became semiconscious, and the fingers were fixed in the obstetric position, being flexed at metacarpo-phalangeal articulations, and extended at interphalangeal joints; thumbs adducted to palms and flexed at metacarpo-phalangeal articulations. Legs stiff, but no plantar flexion. Chovstek's sign strongly positive. Marked hyperpnœa. Some blood was withdrawn from the median basilic vein for chemical analysis, and 8 c.c. of a 5% solution of calcium chloride was injected intravenously. The spasms ceased almost immediately, and respiration returned to normal. Calcium gluconate, 10 c.c. intravenously, was injected on the three subsequent days, and calcium lactate, grm. 5 twice a day, was given by mouth. Ammonium chloride gr. 30 three times daily, was given by mouth for the next fortnight. Nevertheless, on June 15, 16 and 17, slight attacks of carpal spasm occurred, always preceded by a short period when patient complained of tingling in hands, but these attacks were not associated with hyperpnœa. Trousseau's sign positive for three days after initial attack; Chovstek's sign not obtained after June 19. No further attacks of carpal spasm in hospital, although patient complained of tingling in hands for short periods daily until June 26. With onset of tetany there was irregular pyrexia—up to 100° F.—which lasted three days.

Analysis of blood taken on June 14: Serum calcium 11 mgm. per 100 c.c., plasma phosphorus 1·5 mgm. per 100 c.c. Plasma bicarbonate, taken two days later, was 55. Further analysis of blood on June 23: Serum calcium 9·8 mgm. per 100 c.c., plasma phosphorus 4·5 mgm. per 100 c.c. Analysis of stools: Total fat 36·8%, neutral fat 9·09%, saponified fat 10·04%, fatty acids 17·68%.

It is hoped that patient will return to hospital for further investigation of the calcium balance.

Patient was then lost sight of until November 1933. During the four months since her discharge from hospital in July 1933, patient has had no eucortone injections, or extract by mouth. She has remained in good health, apart from a slight gradual loss of weight (4 lb.). Menstruation has continued normal, both in time and amount. Appetite and strength have remained good. No further attacks of tetany have occurred.

Addison's Disease.—DOROTHY C. HARE, C.B.E., M.D., and S. LEVY SIMPSON, M.D.

L. B., female, aged 31, unmarried, was admitted to Elizabeth Garrett Anderson Hospital, December 1923, as a case of "subacute appendicitis," with two weeks' history of pain in right iliac fossa, and vomiting. Similar attacks had occurred three months and three years previously. Laparotomy revealed ileocæcal tuberculous caseous glands. The appendix was normal but was removed. Intermittent pain and vomiting continued. The patient's father had died from pulmonary tuberculosis.

September 1925: Patient readmitted to hospital under Miss Hamilton, with

four months' history of pain in right upper abdomen radiating to right shoulder, attacks of vomiting, diminished appetite, lassitude, and darkening of skin.

On examination.—Tenderness noted in epigastrium, both hypochondria, and lumbar regions. Systolic blood-pressure, 102. Test-meal showed achlorhydria. Wassermann reaction negative. Addison's disease was diagnosed, and suprarenal whole gland tablets were given by mouth without appreciable benefit.

Patient admitted to University College Hospital, July 1929, under Dr. Batty Shaw, with increasing weakness, abdominal pain, vomiting and diarrhœa, 1 st. loss of weight in two years, infrequent and scanty menstruation.

On examination.—Definite pigmentation of skin and lips; systolic blood-pressure varied between 70 and 90 mm. Radiography of chest and suprarenal regions negative.

No specific treatment was carried out and the symptoms continued.

In 1931, patient was admitted to King's College Hospital, under Dr. J. L. Livingstone, with similar chronic symptoms. Systolic blood-pressure ranged between 90 and 100. Blood-count normal. Fresh suprarenal gland given in sandwiches led to a slight improvement.

October 1932: Admitted to the London Hospital under Dr. Robert Hutchison, and observed by one of us (S. L. S.) Faintness, weakness, vomiting and intermittent diarrhœa, loss of weight, and increasing pigmentation were the symptoms at that time. Blood urea, 0·03%; blood-sugar 0·09%. Systolic blood-pressure varied between 100 and 110; diastolic between 60 and 70 mm. Radiography of chest and adrenal area negative. Test-meal showed achlorhydria with total acidity 28. Blood-count: R.B.C. 5,200,000; Hb. 60%; C.I. 0·57; W.B.C. 6,800. *Differential*: Polys. 73%; eosinos. 1%; small lymphos. 15·5%; large lymphos. 5%; large hyals. 5·5%. Eschatin, 5 c.c. intramuscularly, daily, begun on November 22, and within two weeks symptoms had almost disappeared. The patient, however, was irritable and difficult, and the effect of her "emotional storms" on the other patients accelerated her departure. Eschatin 2 c.c. daily continued for two months, but subsequently injections were frequently omitted owing to difficulty of adequate supervision.

March 1933: Blood-pressure 124/84, but patient's condition was not good; yawning and hiccoughs gave rise to some anxiety.

June 1933: Admitted to Elizabeth Garrett Anderson Hospital under one of us (D. C. H.) with persistent symptoms. Characteristic skin pigmentation present, but none on buccal mucous membrane. Systolic blood-pressure, whilst in hospital, ranged between 90 and 110 mm. Blood urea 30 mgm. %. A daily dose of eschatin, 3 c.c., given for four weeks with considerable amelioration of all symptoms.

Patient was then lost touch with until November 1933 when she was again seen by one of us (S. L. S.) Since July she had received no medicine or injections but had continued in fair health until October 1933, when pain in the right loin ascending to the right scapular region was complained of. It has continued ever since, is of a "nagging" character, worse after exertion, but usually noticeable during the night. Lassitude and anorexia have returned.

On examination.—General condition fairly good; marked tenderness in both loins, right greater than left. Blood-pressure 125/90. Pigmentation of moderate degree.

Special points of interest [D. C. H.].—(1) This is a case of proved tuberculous origin, watched for eight years since the diagnosis was made. (2) The asthenic symptoms persist in varying degree, though the blood-pressures have recently been at fairly normal levels. (3) The condition was definitely improved by treatment with extract, and since the injections ceased four months ago, the improvement has been remarkably maintained and the blood-pressure is now 125-90, a higher figure than was ever recorded in daily readings in the hospital during the last period of treatment in June and July 1933.

There is no doubt that cases of chronic and subacute suprarenal deficiency exist without typical clinical signs and symptoms. At the present time there is no

certain means of establishing the diagnosis, and the development of a test for such cases would be of great value. A therapeutic diagnostic test by injection of extract would probably assist but is at present practically impossible owing to the high cost of the extract. There is great need for the stimulation of the wholesale production of concentrated active preparations which could be sold at lower cost.

A Pseudohermaphrodite with Suprarenal Cortical Hyperplasia.—F. W. M. PRATT, F.R.C.S.

Jean R., aged 10½, a well-developed child, muscular, with little body-fat and rather coarse features.

Hair.—Definite excess of dark downy hair on the upper lip; a few sparse hairs on chin. Pubic hair is luxuriant and shows tendency to extend up to umbilicus.

External genitalia: Marked over-development of the clitoris with the urethra opening at its base. Labia majora well developed, but no vagina. Per rectum nothing definite could be felt. Internal genitalia: Laparotomy was performed and it was found that the uterus was very small and continuous with a solid column of tissue representing the vagina. Right ovary normal; left ovary larger than normal; containing a few follicular cysts. Neither uterus nor ovaries were removed.

Suprarenal glands: Right normal in size; left appeared to be slightly enlarged on palpation.

Breasts small and under-developed. Sella turcica normal in size and shape. Blood-pressure 123/70; blood urea 42 mgm.%; urine normal.

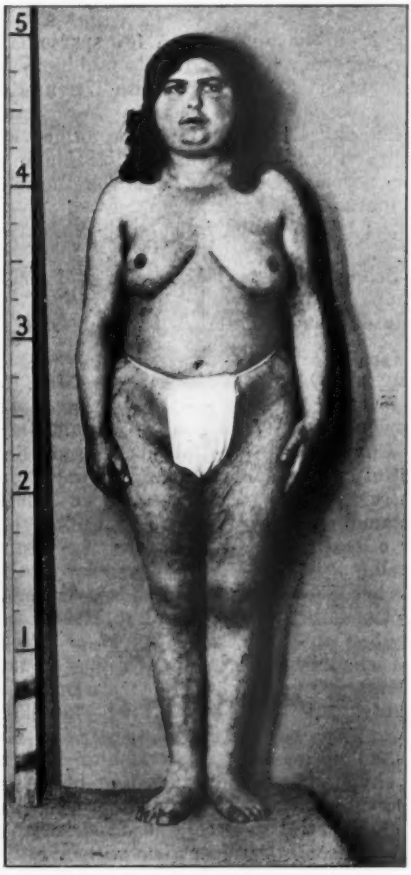
The voice is feminine. The mother states that the child is shy and reserved, and has a strong dislike for boys.

Adreno-genital Syndrome (Cushing type).—CLIFFORD HOYLE, M.D. (for CECIL WALL, M.D.).

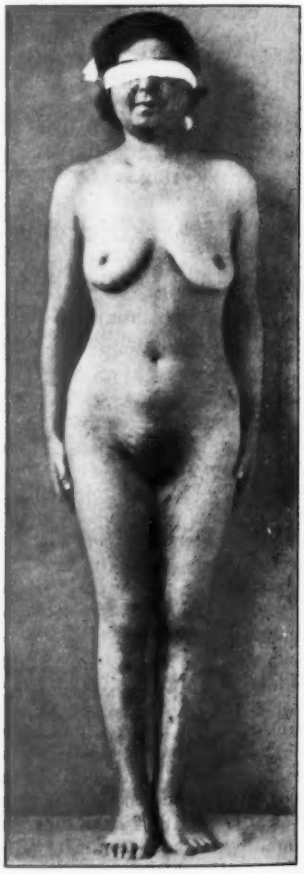
F. T., female, was first seen in February 1932, at the age of 18½, complaining of increasing obesity and amenorrhœa. Childhood uneventful apart from mild attack of typhus fever at 11 and two doubtful attacks of facial cellulitis at 14 and 16. Family history irrelevant. First menstrual period at 12, and subsequently these were regular up to 15, when they became irregular and scanty. Complete amenorrhœa since May 1931. At 15½ noticed rather suddenly that face was getting fatter, and, shortly afterwards, trunk as well. Within a year appearance changed completely. She complained of generalized headaches, insomnia, and loss of mental alertness, with depression. Thyroid extract and diet restriction led to no improvement and her weight increased steadily by 3 st. in three years. At 17 years and 8 months hair appeared on upper lip and shoulders. Examination in February 1932, showed an intelligent girl of short stature and dusky plethoric appearance with considerable obesity of general distribution (weight 10 st. 10½ lb.) (fig. 1). Slight hirsuties of the upper lip and shoulders, upper arms, back, abdomen and thighs, with pubic hair ascending towards the umbilicus. Well-marked striæ atrophicæ over the breasts, axillæ, trunk and thighs, and patchy purplish discoloration of both legs. Blood-pressure constantly raised during observation while at rest and varied between 160/110, and 185/125. Pulse-rate 56 to 84. Retinal vessels and fundi normal. Teleradiogram of heart showed slight enlargement of left ventricle with a rather wide aortic shadow. Electrocardiogram: normal rhythm with left ventricular predominance. External genitalia not abnormal. Urine normal except for trace of albumin. Renal efficiency tests normal and retrograde pyelograms showed both kidneys to be normal. Sugar tolerance raised; fasting blood-sugar 74 mgm.%, and after 50 grm. of glucose this rose to 95 mgm.% in forty-five minutes, and fell to 69 mgm.% in two hours. Blood-count: Erythros. 5,800,000 per c.mm.; Hb. 90%; C.I. 0·77; leucos. 10,000 per c.mm., with a normal differential count. Stereoscopic radiograms of skull normal, except that pituitary fossa was rather small. Blood Wassermann reaction negative. Serum calcium, 10·1 mgm.%; the plasma

phosphorus 3·6 mgm.%. Cerebrospinal fluid pressure normal. The fluid was tested for the presence of an abnormal pressor substance by intravenous injection into a pithed cat, but no such substance could be detected.

Subsequently under the care of Mr. L. R. Broster at Charing Cross Hospital, and of Dr. Gardiner Hill, at St. Thomas's Hospital, where she was treated by deep X-ray therapy to the pituitary body. Later thyroid administration and strict dieting reduced her weight, and this was accompanied by improvement in general symptoms. Under



F. T. February 1932.



November 1933.

observation again at London Hospital, November 1933. General condition improved. Symptoms, apart from amenorrhœa, relieved, and weight has fallen to 9 st. (fig. 2). Obesity now limited more particularly to the face and thorax. The hirsuties has not altered materially but the striæ and patchy purplish discoloration of the breasts and legs are more marked than they were eighteen months ago. The pelvic organs are comparable to those of a girl about puberty except that pubic hairs show

adult development. Blood-pressure now 170/115. Blood-count normal. Serum calcium 10·4 mgm.%, and plasma phosphorus 2·8 mgm.%. Controlled radiograms of the skull, spine, pelvis, femur, tibia, fibula, humerus and radius were normal. Through the kindness of Dr. Donald Hunter the calcium balance was investigated with the following results :—

CALCIUM BALANCE, PER 3-DAY PERIOD.

	Intake	Ca in urine	Ca in fæces	Total calcium
Period 1 (three days)	0·306 grm.	0·42 grm.	0·79 grm.	1·21 grm.
,, 2 (,, ,,)	0·306 ,,	0·55 ,,	0·61 ,,	1·16 ,,
Mean	0·306 ,,	0·485 ,,	0·70 ,,	1·19 ,,

The special points of interest in this patient are the absence of any significant disorder in calcium metabolism, the increased carbohydrate tolerance, and the absence of any pressor substance in the cerebrospinal fluid. A loss of calcium balance with osteoporosis that may even be extreme has been recorded in similar patients but the exact nature of the bone lesions and the mechanism by which they are produced are not understood. Until thorough investigation is done in each case, with an estimation of the calcium balance, controlled radiograms of the bones and careful histological study it is impossible to decide the frequency and nature of the changes. In the present patient, however, calcium balance was slightly negative, the serum Ca and plasma P normal, and the radiographic appearances of the bones normal. Increased glucose tolerance seemed to be exceptional in these patients although obesity is the rule; more often there is glycosuria with diminished tolerance.

The investigation for pressor substances in the cerebrospinal fluid was done with the object of deciding whether the posterior lobe (pars intermedia) of the pituitary body might be concerned in producing the hypertension by secreting pituitrin in excessive amount. The recent emphasis upon abnormalities in the anterior pituitary lobe in these cases also suggested that such might be the explanation. In this case, however, no evidence of this was found. Unfortunately only enough cerebrospinal fluid was obtained to test for pressor activity, but in two other patients with the same clinical condition fuller tests on the cerebrospinal fluid were carried out and in one of these an excess of pituitrin was found by tests for both pressor and melanophore-expanding activity.

Dr. F. PARKES WEBER said that he regarded the case shown by Dr. Hoyle as a typical one of Cushing's syndrome, though there was not evidence of skeletal decalcification. If by any chance the pituitary gland were microscopically examined in serial sections in an exactly similar case, without a basophilic adenoma being detected, he would be inclined to think that Professor Cushing's views on the subject could not be correct.

Two Cases demonstrating the Adreno-genital Syndrome.—ALISON MACBETH, M.B., and S. LEVY SIMPSON, M.D.

I.—B. C., a married woman, aged 28, came to the Walthamstow Clinic for Women a few months ago, complaining of amenorrhœa. She was seen by Miss Margaret Basden, F.R.C.S., to whom we are indebted for permission to carry out investigations and publish our records.

History.—Patient states that she was a thin, poorly developed child. Menstruation commenced at the age of 17, but second menstruation did not occur until one year later. Subsequently menstruation occurred at intervals of nine to twelve months, and lasted three days, but was always very scanty. She thinks that some hair was present on her lips and cheeks at the age of 14, but by the age of 18 there was a well-marked growth of hair on the lips, chin, and sides of the face. At 14 her voice was noted to be very low and deep, several of her friends remarking upon it. She became embarrassed about it and trained herself to speak in a higher tone. Her skin has always been rather dark, but her relatives have remarked that she is getting darker every day.

At the age of 24 (1929) she married. Menstruation occurred on her wedding day, but not again until after the weaning of her child, which was born a year after

marriage. Lactation was inadequate but persisted for six months and was supplemented by bottle feeding. Following weaning there were two menstrual periods at an interval of four weeks; but subsequently the intervals were nine to twelve months. In 1929 she weighed 6 st. 10 lb., but subsequent to parturition there was a gradual increase of weight of 2 st. in four years. Much fat has accumulated in the abdominal region but the limbs remain very spare. The patient is firmly convinced that she is getting "stronger and stronger," and that she cannot possibly get tired no matter how much work she does.

The psychological and emotional attitude in this case is of importance. There is apparently no interest or pleasure in her sexual life; she expresses surprise that she

Adreno-genital syndrome.

ever married and still more so at having a child, a happening which she could never anticipate as possible. She states that she has never felt motherly to her child. Her husband is a first cousin. She has no sexual interest in men, but is equally indifferent to women, although she states that several women are fond of her. During the last few weeks she has been troubled by frequent erections of her clitoris.

Her mother died at the age of 54 in diabetic coma. She had been very thin as a girl, had developed adiposity and a weight of 16 st. in middle life, but lost as much as 10 st. in a period of twelve years preceding her death.

On examination.—A woman of slender build, with dark complexion and deep sunken eyes. Apart from diffuse pigmentation of face there is intensified pigment round the orbits, and considerable dark brown pigmentation on both sides of neck. Pigmentation also at waist-band, slightly along linea nigra and on vulva and groins. Wide black crescent on temporal aspect of left optic disc; otherwise fundi are normal.

There is a growth of hair on the upper lip and chin, and on the side of the face is a specially well-marked growth of black crisp curly hair (mutton-chop) (see fig.). Patient shaves chin and lips every other day. There is a slight extension of the pubic hair upwards on the linea nigra to the xiphisternum and between the breasts. There are also a few hairs around the areolæ. There is a male distribution of hair over the arms and legs, especially on the inner aspects of the thighs, and dorsum of the toes. The hair on the head is moderately plentiful but is falling out to a considerable extent.

Breasts small but well formed. Clitoris and its prepuce quite obviously enlarged. Miss Basden found the uterus smaller than normal and the ovaries were not palpable. Blood-pressure is 120/90; systolic murmur heard in apical region. No other abnormality noted.

Carbohydrate tolerance test: Fasting blood-sugar 0·08%; 45 minutes after 50 grm. glucose 0·162; 120 minutes after, 0·136, Fehling's solution then being reduced by an equal volume of urine. Serum calcium 10·8 mgm.; blood-phosphorus 2·7 mgm. per 100 c.c.; blood-phosphatase 0·154; blood-cholesterol 0·14 mgm per 100 c.c.; blood-urea 0·024 mgm. per 100 c.c. Blood-count: R.B.C. 5,100,000; Hb. 94%; C.I. 0·92, W.B.C. 7,200. *Differential*: Polys. 67%; eosinos 3%; small lymphos. 22%; large lymphos. 6·5%; large hyals. 1·5%. (Several of these investigations were carried out by courtesy of Dr. R. A. Rowlands.)

Radiographic examination (M. Jupe).—Both kidneys well seen, but nothing abnormal detected in the adrenal areas; the sella turcica appears normal.

Treatment.—From November 5 to 14, 10,000 units menformon (folliculin), were injected daily intramuscularly. On November 22, a menstrual period of twenty-four hours occurred with mucous discharge (the previous spontaneous menstrual periods were October 18, 1933, and December 1932). Injections were resumed on November 24 (15,000 units daily for five days). During the last three weeks the patient is of the definite opinion that the hair on the face has increased in amount, and that the breasts are much larger. There have also been frequent erections of the clitoris.

II.—B. B., a married woman, aged 27, first attended the Mildmay Mission Hospital in June 1933, on account of sterility and amenorrhœa. She came under the care of Miss Margaret Basden, F.R.C.S., to whom we are indebted for permission to carry out investigations and publish our records.

History.—Patient had been a well-developed child. First menstruation noted at age of 15. For the next two years menstruation occurred at intervals of seven or eight weeks, and lasted four days. Subsequently the intervals became longer, varying from four to nine months, the discharge being scanty and lasting a few days.

Married at age of 21. During next seven months weight increased from 8 st. 6 lb. to 13 st. From then up to date there has been a further slight increase of about ten pounds, despite thyroid therapy. Patient thought she was pregnant seven months after marriage and made preparations for childbirth. Condition apparently a pseudo-cyesis, partly attributable to enormous increase of abdominal fat. No abnormality as regards growth or distribution of hair until two years ago. In 1931, hair began to grow on upper lip, sides of face and chin. Some months later the pubic hair appeared to extend upwards towards the umbilicus.

Family history.—Mother died, aged 58, from diabetes mellitus, which she was known to have had for eight years. She apparently grew very fat in middle life, weighing 19 st. a few years before death. Patient's eldest sister, aged 38, has

hirsuties of similar distribution to that in her own case, but of unknown duration. Until recently she has had scanty and infrequent menstruation (intervals of five months), but nevertheless has two children.

On examination.—An obese, comely woman with ruddy cheeks and well-developed breasts. Fine moustache with soft short dark hair on either side of cheeks in front of and below the ears. Also some fine hair just below lower lip on point of chin and in fat folds of neck below. The pubic hair is luxuriant, and ascends upwards to the umbilicus in a wide triangle of short straight soft dark hair. Further but less well-marked extension upwards to the xiphisternum and some hair in the intermammary region. Coarse hair covers arms and legs, tending to be of male distribution, especially involving inner side of thigh, and occurring in little tufts on dorsal aspects of toes. Hair on head black and luxuriant, but falls out to a slight extent.

In lower half of abdomen, also laterally on flanks, are vertical lineæ distensæ converging slightly downwards and medially. Blood-pressure is 154/80. Pulse 76. Systolic murmur at apical region. Some slight pigmentation over waist-line, at vulva, and inner aspects of the thigh. Fundi normal.

A pelvic examination was carried out in June 1933, by Miss Basden, who found the body of the uterus to be abnormally small. Otherwise nothing abnormal was noted. A second examination made recently by Miss Basden showed the uterus to be slightly larger than previously; both ovaries, however, were now somewhat enlarged, but no definite cystic follicles could be palpated. It should perhaps be observed at this point that the patient had been receiving injections of menformon (folliculin) and pregnyl (gonado-tropic hormone of pregnancy urine) for a period of some weeks previous to the second gynæcological examination. (Two menstruations occurred during this period of treatment.) The clitoris at no time appeared to be of abnormal size.

Carbohydrate tolerance test: Fasting blood-sugar, 0·11; 30 minutes after 50 grm. glucose by mouth, 0·15; 60 minutes after, 0·18; 90 minutes after, 0·16; 120 minutes after, 0·14; at no time was glycosuria present. Blood-count: R.B.C. 4,900,000; Hb. 100%; C.I. 1; W.B.C. 6,000. *Differential:* Polys. 54·5%; lymphos. 41%; large monos. 2·5%; eosinos. 1·5%; basos. 0·5%.

Comment [A.M.].—These two cases have certain features in common, although the second patient (Case II), unlike the first (Case I), has normal feminine emotional reactions, is interested in her sexual life and hopes to have a child. The mothers of both patients grew fat in middle life and died of diabetes mellitus. The family history in Case II has an additional feature of interest, the sister of the patient also showing hypertrichosis associated with incomplete amenorrhœa. There was a tendency to hypertension in patient (II), and in both patients (I and II), there was some evidence of impaired carbohydrate tolerance.

Specimens and Clinical History of a Case of Renal Aplasia with Cortical Adrenal Hyperplasia.—REGINALD LIGHTWOOD, M.D. (by permission of R. S. FREW, M.D., and E. A. COCKAYNE, D.M.).

The patient from whom these specimens were taken died, aged 3 years and 4 months, after being under clinical observation for nearly two years. His case was demonstrated in 1931 before the Section for the Study of Disease in Children, under the title of "renal rickets."

He was prematurely born, weighing 3 lb. 8 oz., and when aged 1 year and 5 months was brought to the Hospital for Sick Children on account of vomiting and failure to grow. The urine contained albumin, and a diagnosis of renal rickets was established by radiology. At that time the blood-urea was 77 mgm. per 100 c.c. serum calcium 12·3 (normal 9 to 11), blood-phosphorus 7·2 (normal 4 to 4·5), urea

concentration impaired, Wassermann reaction negative. The skin had the brownish-yellow colour rather characteristic of renal rickets.

In 1932, he attended the London Hospital, but in the following year was brought back to the Hospital for Sick Children, and readmitted for study. By this time his general appearance had altered strikingly, even allowing for age-changes (he was then aged 2 years and 10 months). In addition to the brownish sallowness, there was an unusual plumpness about the upper part of the body, and slight hirsuties; the genitalia were normal. The child was stunted and very rachitic. Subsequently the obesity of thorax, arms and face increased, as did the hairiness, and a fine tremor of the head and arms appeared. Despite a urea retention of over 200 mgm. % he remained remarkably cheerful. He died six months later from a staphylococcal infection.

CHIEF BIOCHEMICAL FINDINGS (Dr. W. W. PAYNE).

	Observations varied from	Normals
Blood serum calcium	10 to 12·3 mgm. %	9 to 11
Inorganic blood-phosphorus ..	4·6 to 7·2 mgm. %	4 to 5·5
Plasma phosphatase ...	7·2 to 9·7 units	5 to 15 units
Plasma chloride	0·550%	0·561 to 0·632
Blood-cholesterol	168 mgm. per 100 c.c.	100 to 200
Blood-urea	77 to 254 mgm. per 100 c.c.	15 to 40

Post-mortem examination.—(Significant findings only reported.) Pale, yellow-coloured, with subcutaneous bruising. Hairiness of chest, limbs and neck. Excess of fat affecting face, neck, upper arms and trunk. Length 2 ft. 2 in., weight 23 lb.

Heart enlarged, showing concentric hypertrophy of left ventricle; weight 50 grm. Great excess of fat in abdomen, omentum, mesentery, &c. Kidneys: small and sclerotic, embedded in fat. Excess of fat around renal pelvis. Cortex reduced in width and normal differentiation diminished. Capsule striped easily showing a slightly granular surface. Suprarenals: Diffuse hyperplasia. The combined weight of the suprarenals was greater than that of the kidneys. The other endocrine glands showed no demonstrable abnormality. Vessels normal. Bones showed gross deformity, decalcification and active rachitic changes. The bone-marrow was somewhat sclerotic and pale. It was noted that the subcutaneous fat about the upper part of the body was not unlike beef-suet: I have only seen this type of fat in children who have died with hyperplastic disturbances of the adrenal cortex.

Histology.—Kidneys: Numerical reduction in glomeruli of which some were normal, others showed capsular dilatation, proliferation, fibrosis, etc. Dilatation of many tubules to which the presence of albumin casts gave the appearance known as "thyroidization of the kidney." Some of the convoluted tubules showed a low type of undifferentiated epithelium with the nuclei almost filling the cells. Some tubules were surrounded by a spindle of fibrous tissue. There were a few intratubular calcium deposits. Gross interstitial fibrosis and interstitial infiltration with lymphocytes, fibroblasts and endothelial cells. Adrenals: Uniform increase of all layers of the cortex and some individual increase in the size of constituent cells. Increased lipoid content with signs of degeneration. No increase of medullary elements

Pseudohermaphroditism and Suprarenal Hyperplasia.—R. W. B. ELLIS, M.D. (by permission of Dr. HUGH THURSFIELD).

Specimen from an infant aged 8 months.

Clinical history.—Full term, normal delivery, birth weight 8 lb. 9 oz. Born with penis and scrotum of approximately normal size. One sister (aged 6½) is well; mother has had no other pregnancies. Breast-fed for five weeks; then repeated changes of feeding on account of vomiting and loss of weight. Thought to have had pain on micturition. Admitted to hospital, 27.7.33, aged 16 weeks, on account of wasting. It was then noted that there was a first degree hypospadias, and that the testicles were undescended. The weight was 8 lb. 3 oz., and there was considerable dehydration. Whilst in hospital the infant failed to respond to treatment, which included continuous intravenous saline injections and five blood-transfusions. After

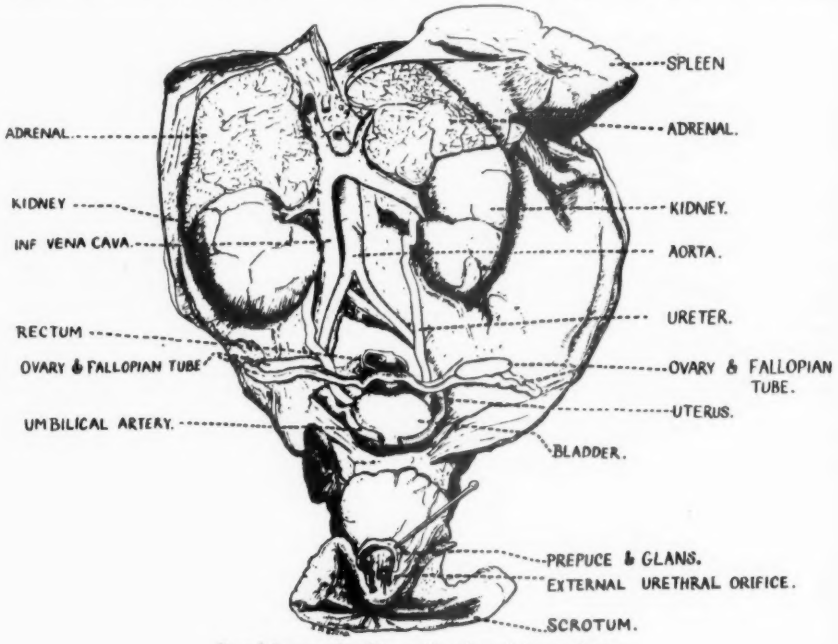
a very slow gain in weight of 9 oz., it lost weight until death occurred 10.11.33. Vomiting was frequent, unaccompanied by diarrhœa, throughout the four months the infant remained in hospital.

Blood-count (17.10.33): R.B.C. 4,300,000; Hb. 70%; C.I. 0·8; W.B.C. 8,000. *Differential*: Polys. 46%; lymphos. 50%; monos. 3%; eosinos. 1%.

Urine contained albumin on repeated examination, but only occasional red blood cells and no casts.

Blood-urea (27.7.33) 138 mgm.%, falling rapidly to 70 mgm.% (31.7.33). Subsequent estimations ranged between 27 mgm. (20.9.33) and 78 mgm. (a week before death).

Report on specimen.—The genito-urinary organs, adrenals, spleen, rectum, and anus have been removed *en bloc*. There is considerable hypertrophy of both adrenal



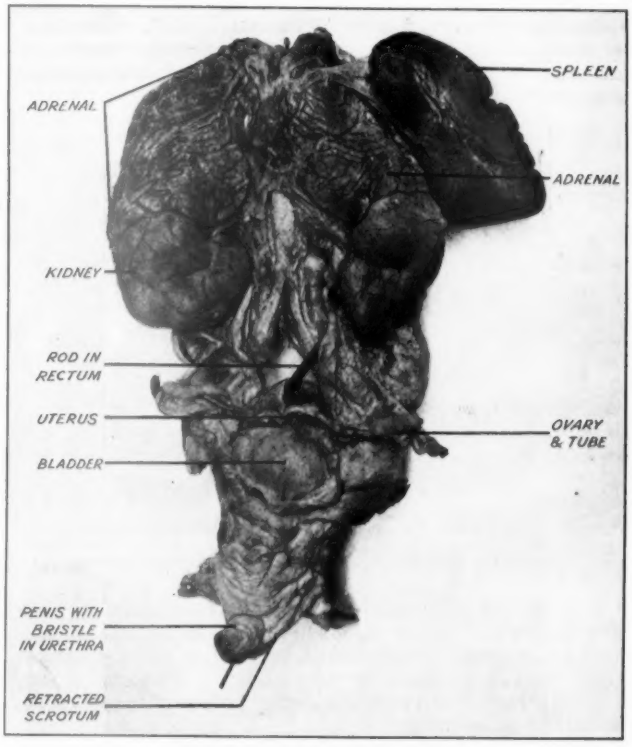
Pseudohermaphrodite, with adrenal hyperplasia.

glands, particularly of the right, which is more than twice the normal size; the right measures 6 cm. by 4 cm., and the left 4·5 cm. by 3 cm. Their normal shape is retained, but the surface is thrown into an excessive number of fine folds. Both kidneys show some evidence of fœtal lobulation; the ureters and bladder are normal.

There is a uterus, with Fallopian tubes and ovaries of normal size for age; the uterus has a well-formed cervix, and connects with a vagina which ends blindly at its lower end, approximately 0·3 cm. above the perineum. The vaginal orifice is represented by a dimple in the perineum.

The external genitalia are those of a male with first degree hypospadias and absence of testicles. A bristle has been passed into the urethral orifice which lies at the base of the glans. There is a well-formed penis and small scrotum with rugæ, median raphe, and septum. There are no testicles or prostate present.

Microscopical section of the right adrenal shows no derangement of general structure, though there is some separation of the cortical cells. The condition appears to be a simple hyperplasia of the whole gland. Section of the right ovary shows the normal appearance of the infantile ovary. Section of the right kidney shows considerable congestion in the pyramidal region, with some hyaline degeneration of the tubules.



Pseudohermaphrodite, with adrenal hyperplasia.

Comment.—From the type of gonad, the subject must be regarded as a female having undergone masculinization from hyperactivity of the adrenal glands; these are obviously hyperplastic. The conversion of the clitoris into a penis and the labia into a scrotum is singularly complete. Thus, the urethral orifice is situated at the base of the glans, and not at the base of the penis as occurs in the less complete cases. That the condition was operative during intra-uterine life is shown by the male character of the external genitalia at birth.

Specimen from Case of Suprarenal Hæmorrhage following Breech Delivery. R. W. B. ELLIS, M.D. (by permission of Dr. HUGH THURSFIELD).

Clinical history.—Full term, after normal pregnancy. First child. Breech delivery, taking one and a half hours. Convulsive twitchings of face began a few minutes after birth. Infant admitted to hospital 7.11.23, aged 7 hours. At this time, the infant was moderately cyanosed, with irregular feeble respiration and

recurrent twitchings of face; right thigh and foot swollen and blue. Spasticity of both lower limbs and of left arm. Died, with respiratory failure, twenty-four hours after admission.

Post-mortem examination showed an area 3 cm. diameter of subperiosteal hæmorrhage on surface of left parietal bone, and a very extensive right-sided tentorial tear, the whole of the right margin of the tentorium being separated from its attachment. Large mass of dark blood-clot (5 cm. diam.) immediately above and posterior to the cerebellum, and several drachms of dark fluid blood in posterior cranial fossa; blood-stained cerebrospinal fluid in ventricles. Contusion of adductor and flexor muscles of right thigh. Both lungs engorged, with scattered patches of atelectasis throughout, principally right and left bases.

Bilateral suprarenal hæmorrhage following breech delivery.

Specimen.—Large area of hæmorrhage (1·5 by 2 cm.) seen involving the lower half of the anterior surface of the right suprarenal, which latter measures 3 cm. by 3·5 cm. The upper pole has been removed for section, and the hæmorrhage is here seen to extend throughout the medullary region. There is a smaller area of hæmorrhage (0·5 by 2 cm.) seen on the anterior surface of the left suprarenal. The kidneys show fœtal lobulation.

Section (hæmatoxylin and eosin).—Extensive areas of hæmorrhage involving both cortical and medullary regions, with disorganization of normal structure. Medullary cells stain poorly and in several instances show granular degeneration.

History of a Case of Carcinoma of the Adrenal Cortex with Cushing's Syndrome.[1]—F. G. LESCHER, M.C., M.D., and A. H. T. ROBB-SMITH, M.B.

Ivy C., aged 35, was sent by her doctor to the Derbyshire Royal Infirmary, in November 1932, complaining chiefly of dull pain in chest and legs, and some shortness of breath on exertion. No past illness. One healthy child born fourteen years ago. In 1929, menstruation, which had always been regular, ceased.

Until about two years ago had been slim, but since then had grown stouter; face and body had become dusky red, with some dryness of skin. In 1931 she noticed that though hair of scalp was falling out, hair had begun to grow on the

[1] A brief account of this case, with a report of the pathological findings, was communicated to the Section of Therapeutics and Pharmacology at the meeting of November 14, 1933, when a discussion on "Suprarenal and Pituitary Tumours" was held (*Proceedings*, 1933, xxvii, 271, Sect. Therap., 17).

upper lip and chin. She thought that lately she had become more hungry and thirsty than usual, and passed more urine ; also noticed that she bruised more easily. No undue weakness, and in spite of her disabilities, could do her ordinary work fairly well. No headaches or palpitations. No difficulty in swallowing, or sense of suffocation. No subjective symptoms in her limbs such as a creeping or burning sensation.

Family history.—Nothing of importance.

On examination.—A fat, plethoric, round-shouldered woman of a striking purplish-red complexion. Weight 8 st. 10 lb. ; height 5 ft. Fat was evenly distributed over face, neck and trunk, the extremities having escaped. In fact, the feet and hands were quite small. No local tender collections of fat.

Face, trunk, and extremities florid and cyanosed. Cyanosis especially marked on face, forearms, legs, and upper part of chest. A large bruise on upper and outer part of right thigh. No purpuric spots, and on constricting the arm none were seen below. Skin dry, especially over legs, and in this situation somewhat of the texture of parchment. No œdema or pigmentation of skin, except on front of abdomen and on upper parts of thighs, where pigmented striæ atrophicæ were seen.

Hair on scalp thin, especially over forehead ; normal on eyebrows. Axillary and pubic hair rather increased in amount : the latter was of feminine distribution. Coarse growth of hair on upper lip and chin, causing a somewhat masculine and virile appearance ; also hair round the nipples, but no hirsuties on cheeks or rest of body.

No exophthalmos, no enlargement of thyroid, no tremor of hands, but pulse-rate ranged between 100 and 110, when patient was at rest, and was regular.

Heart enlarged ; apex beat felt in fifth space, four inches from mid-sternal line. This was confirmed by a teleradiogram. First sound booming at apex ; second accentuated at aortic base. Electrocardiogram showed inversion of T_1 and T_2, with left-sided preponderance. Blood-pressure was 205/155. This was examined on many occasions to exclude the possibility of the condition being paroxysmal. Radial and brachial arteries not felt to be thickened. No evidence of disease of bronchi or lungs.

Patient complained of indefinite pain in epigastrium and left renal region, but palpation of abdomen revealed nothing abnormal—such as a swelling, or resistance —suggestive of suprarenal tumour, nor could the kidneys be palpated.

Neuromuscular system : nothing abnormal, except that fundi showed blurring of the disc edges, the right nasally, the left nasally and temporally. No hæmorrhages into the retinæ seen. Visual fields normal (Mr. C. H. Bamford). No local or general muscular weakness.

External genital organs normal, with normal pubic hair of feminine distribution. Clitoris not enlarged. Uterus subnormal in size, the cervix being atrophic. The ovaries could be palpated. The atrophic changes could be explained by post-menopausal atrophy. No evidence of any change towards masculinity (Mr. N. L. Edwards).

During patient's stay in hospital, no undue increase in fluid intake or output was noticed, and there was no change in the appetite.

She was a cheerful, mentally alert woman, though self-conscious of the hair on the face, and of her ruddy complexion. Not drowsy. Did not complain of headache or giddiness. Her mental outlook remained feminine.

Urine : Trace of albumin, but no casts. Sugar found, but no ketonuria. Concentration for urea : first hour 2·4% ; second hour, 2·7%. The Aschheim-Zondek test on the urine was negative. No indication of increased hormonic output with regard to either ovarian or anterior lobe hormones, the uterus and ovaries of the experimental animals having remained quite infantile.

The following were the results of the first examinations of the blood. They were repeated on various occasions with much the same results :—

Hb. 150% ; R.B.C. 6,920,000 ; W.B.C. 16,000. *Differential :* Neutros. 84% ; lymphos. 13%. No abnormal red cells.

Fasting blood-sugar	228·0	All values in mgm. per 100 c.c. of blood.
1 hour after taking 50 grams of glucose	286·0	
2 hours after taking 50 grams of glucose	261·0	
Blood-urea	32·0	
Serum calcium	10·1	
Serum cholesterol	148·0	
Serum phosphorus	2·4	

Calcium and phosphorus examinations.—She was given a diet containing 0·97 grm. of calcium, and 1·08 grm. of phosphorus per day. After being on this diet for four days, the excretions were studied for the next three days, the periods being marked off by carmine, with the following results:—

Calcium.

Period	Urine grams	Fæcal grams	Total Output grams	Total Intake grams	Balance
Three days.	1·13	2·32	3·45	2·91	−0·54

Phosphorus.

Period	Urine grams	Fæcal grams	Total Output grams	Total Intake grams	Balance
Three days.	1·20	1·01	2·24	3·25	1·01

On a diet containing 100 grm. of carbohydrate, with an unrestricted amount of protein and fat, increasing doses of insulin did not appreciably lower the blood-sugar. On units xxx twice daily, the blood-sugar, three hours after a meal, was 224 mgm. %.

Radiological report (Dr. R. A. Laurie).—Most bones of the trunk show a generalized decalcification.

(1) The ribs on both sides show multiple fractures, with considerable callous formation.

(2) The left ischial ramus shows an old united fracture.

(3) There is partial collapse of the 6th, 7th and 8th dorsal vertebræ.

(4) The radiological appearances are not suggestive of either generalized osteitis fibrosa, or metastatic carcinoma.

(5) The pituitary fossa appears normal.

(6) The shadow in the left renal region is probably a partially calcified suprarenal tumour, which may account for the high position of the left diaphragm, and the low position of the left kidney, as shown in the pyelogram, the calyces in which appear normal.

Operation (June 10, 1933).—Mr. G. Dyke removed a left suprarenal tumour about 6 in. in diameter. The patient's condition after operation was satisfactory for about twelve hours. The temperature then rose to 106°; the pulse-rate increased and the patient died.

Pathological report (A. H. G. ROBB-SMITH).—The tumour weighed 593·0 grm. It was of a yellowish colour, covered by a thin capsule through which it appeared to be breaking in places. No remains of the suprarenal body could be seen. The cut surface showed a solid yellowish growth in which there were areas of hæmorrhage and degeneration. Microscopically the tumour has the appearance of an adrenal cortical carcinoma.

The right suprarenal gland appeared to be natural.

All the bones examined showed an extreme degree of osteoporosis and some callous formation in the region of the fractures.

The bone-marrow showed evidence of active erythropoiesis.

The uterus and ovaries were atrophic and had the appearances of typical post-menopausal organs.

The pituitary gland was of normal size, but a differential count of the cells showed an increase of basophil cells, and in one place there was a collection of basophil cells 0·3 mm. in diameter, but it is doubtful whether this can be regarded as an adenoma.

Section for the Study of Disease in Children

President—F. C. PYBUS, M.S.

[*November* 24, 1933]

Some Renal Abnormalities

By O. L. ADDISON, F.R.C.S.

CONGENITAL abnormalities of the genito-urinary tract are extremely common, and are the most frequent of all congenital abnormalities. Many of them are unimportant and give rise to no symptoms and may be discoverable only on post-mortem examination; on the other hand a large proportion lead to serious ill-health or death at an early age.

Ectopic kidneys, single kidneys, horse-shoe kidneys, and double kidneys are not infrequent, and the two last are specially liable to form hydronephroses. Double ureters on one or both sides, each having its separate pelvis and calices, are not uncommon and unless there is some obstruction to the outflow of urine, cause no symptoms. Generally the ureters join and enter the bladder by a single opening, though two openings on one side are not very uncommon. Four separate openings are very rare. A double ureter is often associated with a stricture in some part of its course, causing a hydro- or pyonephrosis.

Hydronephrosis due to congenital abnormalities is seen in three forms.

The closed type due to atresia of the ureter at the junction of the pelvis and ureter, or to non-development of the whole ureter, is unilateral, often of very large size, and may occupy nearly the whole abdomen. It may be noticed at birth. This type gives rise to no symptoms as a rule and very seldom becomes infected, probably because there is little or no secreting tissue left.

The intermittent type, also due as a rule to a partial obstruction at the pelvi-ureteric junction, is generally unilateral, but may be bilateral and seldom reaches a large size. The obstruction may be due to a valve formed by a redundancy of the mucous membrane of the ureter. Valves of the mucous membrane are normally present in the fœtus and usually disappear by the third month. More often the obstruction is due to a kink of the ureter or an aberrant renal vessel passing to the lower pole.

The open type of hydronephrosis is associated with a megalo-ureter and is frequently bilateral. The obstruction may be in any part of the ureter, but is most often at the lower end.

Sometimes the obstruction is due to a pinhole opening in the mucous membrane of the bladder, and in this case the lower end of the ureter becomes prolapsed into the bladder and forms a ureterocele, a smooth rounded swelling projecting into the bladder at the site of the ureter. The actual opening of the ureter may be anywhere on the swelling.

In some cases of bilateral megalo-ureter and hydronephrosis, no mechanical obstruction can be found, even on post-mortem examination, and it seems probable that this type is due to a neuromuscular defect in development. It is always present in cases of absence of the muscles of the anterior abdominal wall, and I have also seen it in cases of Hirschsprung's disease.

Another common cause of bilateral megalo-ureter, and hydronephrosis with dilatation of the bladder, is congenital obstruction of the urethra by valves of the mucous membrane in connexion with the verumontanum. A congenital obstruction of the female urethra by a diaphragm has been recorded, but is extremely rare.

Megalo-ureter and hydronephrosis are much more liable to infection than the closed or intermittent type of hydronephrosis, and are usually heavily infected with *Bacillus coli* by the time they come under observation.

Renal Rickets with Calcification in the Kidneys.—NORMAN B. CAPON M.D.

M. M., female, aged 11 years.

Parents healthy; one brother, aged 9 years, quite well.

Patient's history.—Full-term baby: breast-fed. Measles when aged 5 years, followed by chicken-pox. Periodic attacks of malaise, loss of appetite, foul breath, constipation, and abdominal pain. She was first seen (in her home) at the age of 5 years and 10 months: she was then recovering from one of these attacks, in which there had also been some fever. Examination showed her to be a thin pale child, with mild urinary infection, the urine containing a moderate amount of albumin, fairly numerous pus cells, an occasional erythrocyte, but no casts or crystals. Another examination of the urine one week later showed that the infection had almost cleared up, and there was only a trace of albumin.

When 7 years old she was in the Stanley Hospital, Liverpool, and Dr. Wadsworth (to whom I am indebted for clinical notes) regarded the case as suggestive of diabetes insipidus. The daily output of urine was about 200 oz., but the injection of pituitrin did not cause any reduction. The skull skiagram was normal. The blood non-protein nitrogen was 35 mgm. per cent., and the urea percentage in the urine was found to reach 2·05% three hours after a meal.

Her present complaints are of thirst and polyuria for about six years, headaches, and shooting pains in the limbs for one year and inability to walk for nine months. There is no clear history of hypervitaminosis.

Present condition.—An undernourished child of moderately good colour and bright mentality. Weight 35 lb. Height 40 in. Pigeon-chest; slight scoliosis: genu valgum. Some dental caries. Pulse 72. Systolic blood-pressure 80. Heart of normal size; heart-sounds normal. No arteriosclerosis or X-ray evidence of calcification in the arteries. Optic fundi normal. No evidence of parathyroid abnormality.

Urine.—Daily volume 70 to 116 oz. Very pale urine usually containing a trace of albumin, but no sugar or acetone. Specific gravity generally between 1002 and 1010. Pus cells always present, and sometimes a few erythrocytes and triple phosphate crystals. No casts. Many coliform organisms.

Urea percentage, resting, 0·55%; after 15 grm. of urea had been given orally, the percentage rose as follows:—

1 hour 1·05%. 2 hours 1·35%. 3 hours 1·5%.

Fixation of specific-gravity test showed variation from 1000 to 1010.

Phenol-red excretion:—

½ hour	after injection	125 c.c.	urine	3·3% of dye
1½ hours	„ „	75 c.c.	„	55·8% „ „
2½ „	„ „	50 c.c.	„	35·0% „ „

Blood.—Non-protein nitrogen 39 mgm. %.

Calcium on	September 6	..	9·8 mgm. %
,, ,,	November 30	..	11·3 ,, ,,
Phosphorus	September 6	..	2·2 ,, ,,
,,	November 30	..	4·93 ,, ,,

Wassermann reaction negative.

Fæces.—Total fat .. .. .. 19·7% of dry fæces

Neutral fat	.. .. ..	6·63%
Soaps	.. .. ..	8·8%
Fatty acids	.. .. ..	4·27%

} of total fat

X-ray examinations.—Kidneys: Calcareous deposits in the calices of both kidneys and pelves of both ureters. Calcified glands in right side of abdomen.

Calcification in the kidneys.

Uroselectan given on two occasions: a large amount of dye seen in the bladder but none in the kidneys or ureters.

Bones: Skull negative. Changes at diaphyses, suggesting renal rickets. Fractures, in process of repair, in middle third of both fibulæ, and at junction of upper and middle third of the ulna of both arms. Delayed ossification of epiphyses and of the carpus. The bones are smaller and more translucent than those of a healthy child of same age.

Discussion.—DR. REGINALD LIGHTWOOD said that members of the Section would be grateful to Dr. Capon for having brought forward such an important case. The question of

pathological calcification in the viscera, the vessels and elsewhere in infants and children, was imperfectly worked out and occurred in at best five groups of cases.

1.—In *renal rickets* lime deposits had been reported by Karelitz and Kolomoyzeff [1] in a boy aged 11 years. In this instance there had been intra-abdominal calcification and the arteries were affected. In a more recent case Smyth [2] had described post-nephritic renal dwarfism complicated by progressive calcification of the arteries and dura mater at the age of 14 years; the post-mortem examination in this case showed calcinosis of the kidneys and other viscera, and the parathyroids were grossly hyperplastic. He, Dr. Lightwood, [3] was presenting at the Clinical Section a case of renal rickets in which small deposits of calcium had occurred in association with skeletal demineralization. Karelitz and Kolomoyzeff believed that the pathological calcification they described was the effect of viosterol given therapeutically for the rachitic condition.

2.—In *hypervitaminosis-D*, calcification of the kidneys and vessels had occurred in experimental animals [4, 5, 6] and similar effects had resulted after large doses of parathormone [7]. Cases of infants believed to have suffered from hypervitaminosis-D had been published [8, 9], but the doses of the vitamin had not much exceeded the recommended therapeutic amounts [10], so that the question of intolerance had been raised. The mineral deposits in such cases were intra-tubular.

3.—In *Albers-Schönberg's* disease pathological calcification affecting the vessels and viscera might occur [11]. The osseous changes, however, were quite distinct from those seen in Dr. Capon's case.

4.—In four cases of infants aged between six and ten months, who had failed to thrive and manifested renal failure, he (Dr. Lightwood) had found tubular infarcts of calcium salts; he had applied the term *calcinosis infantum* to this condition [12]. The explanation of these cases might lie in a disturbance of the calcium metabolism, resulting in blockage of the tubules during an unsuccessful attempt to excrete an excess of non-utilizable mineral. Sometimes he had found the deposits in the arteries as well.

5.—*Subcutaneous calcinosis* [13] was recognized in childhood as in adults. Often it took the form of lime deposits in the subcutaneous tissues and around the joints, but also sometimes in the muscles. Deformity and invalidism might result and spontaneous recovery had been reported [14].

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Mr. A. Ralph Thompson said that he had come across two cases—in sisters—of the formation of crystals in both kidneys. The girls were aged about seven and five years respectively. They had delicate features, but were undersized. The eldest had been operated upon for a ureteric calculus, and later passed more stones, chiefly from the left side, the ureteric stone having been removed from the right ureter. She was admitted to a fever hospital with a mild attack of diphtheria, and unexpectedly died. On section of the kidney it was found to contain within its tubules numerous crystals, the exact nature of which is still to be determined. Later on the sister was admitted to Guy's Hospital, and died with symptoms pointing to nephritis. On section a condition was found precisely similar to that in the elder sister. The right femur was found to be normal in every way, with no alteration from the normal epiphysial formation. In neither of the sisters was there any evidence of rickets.

Two Cases of Chronic Pyuria treated with Autogenous Vaccines.—BERNARD SCHLESINGER, M.D.

(I) M. P., a girl, now aged 9 years, had suffered intermittently for over one year with chronic pyelitis with bouts of high fever, the urine culture at first showing *B. coli* and later changing to *B. proteus*.

Investigations by cystoscopy (Mr. Kenneth Walker), *uroselectan and radiography* showed no structural abnormality of the renal tract. Calculus and tuberculosis were also excluded.

Treatment and course of disease.—The usual treatment with alkalies, hexamine and caprokol in turn, produced no permanent benefit. Ketogenic diet for a fortnight made the condition much worse. Treatment with an autogenous vaccine made from *B. proteus vulgaris* was given weekly for five months (Dr. Ellison). The child's general condition rapidly improved, there was steady gain in weight, and the periodic pyrexial attacks ceased. The pus in the urine rapidly diminished and finally disappeared. The urine culture, however, has never been sterile, but latterly *B. coli* has replaced *B. proteus*. Vaccine therapy caused no local or general reaction.

DETAILS OF VACCINE THERAPY AND URINE EXAMINATION.

Date	Dose of vaccine	Date	Urine
		30.4.32	Pus +++ *B. coli*
		3.5.32	Pus +++ *B. proteus*
		26.8.32	Pus ++ *B. proteus*
19.9.32	400,000		
26.9.32	800,000		
3.10.32	1,600,000		
10.10.32	2,400,000		
17.10.32	3,200,000		
23.10.32	4,000,000		
31.10.32	5,000,000	31.10.32	Pus + *B. proteus*
7.11.32	8,000,000		
14.11.32	8,000,000	14.11.32	No pus cells, *B. proteus*
21.11.32	10,000,000		
29.11.32	10,000,000		
5.12.32	15,000,000		
12.12.32	15,000,000		
19.12.32	20,000,000		
9.1.33	20,000,000		
16.1.33	30,000,000	14.1.33	Very occasional pus cell, *B. proteus*
23.1.33	50,000,000		
30.1.33	70,000,000		
7.2.33	70,000,000		
13.2.33	100,000,000		
20.2.33	100,000,000		
Vaccine stopped		2.3.33	Very occasional pus cell, *B. proteus*
		5.3.33	No pus, *B. proteus*
		10.7.33	No pus, *B. proteus*
		13.10.33	No pus, *B. coli*

(II) M. G., a girl, now aged 10 years, from 1928 to 1931 had repeated attacks of *B. coli* pyuria with severe symptoms: headache, vomiting, pain in the loins and high fever.

Investigations.—Uroselectan given intravenously revealed a rare congenital abnormality: four ureters. Cystoscopy (Mr. Kenneth Walker) confirmed this, and demonstrated four openings into the bladder. A pyelogram (Mr. Addison) showed the nature of the abnormality more fully: there are four pelves, four ureters, and four openings into the bladder. The urea concentration in the urine was slightly below normal: the blood urea was 25 to 50 mgm. per 100 c.c.

Treatment with alkalinization and urinary antiseptics (hexamine, caprokol, etc.) failed to improve the condition permanently. Ketogenic diet only had a transient beneficial effect. An autogenous *B. coli* vaccine was prepared and given for nine months at weekly intervals (Dr. Signy). Local and general reactions were

encountered, which lasted for about twenty-four hours. The urine finally became sterile and pus disappeared. The general condition has greatly improved and the child has been free from symptoms for the last nine months.

DETAILS OF VACCINE THERAPY AND URINE EXAMINATION.

Intervals of injection	Dose of vaccine		Date	Urine	
			9.9.32	Pus	*B. coli*
From 7.10.32 at weekly intervals	2,000,000				
	5,000,000				
	7,500,000				
	10,000,000				
	15,000,000				
	25,000,000				
	50,000,000				
	75,000,000				
	100,000,000				
	125,000,000		9.12.32	Pus	*B. coli*
	150,000,000				
	200,000,000				
	250,000,000	Local arm reaction. Temp. 100·3°			
	250,000,000	Local arm reaction. Pyrexia			
	150,000,000				
	200,000,000				
	250,000,000				
	300,000,000				
10.2.33	350,000,000		10.2.33	A few pus cells	Sterile
17.2.33	400,000,000				
24.2.33	450,000,000		24.2.33	Pus	*B. coli*
	500,000,000	Reaction. Temp. 101°			
	500,000,000	Reaction. Temp. 101°			
	500,000,000	Reaction. Temp. 102°			
	400,000,000				
3 weeks interval then ...	450,000,000				
3 weeks interval then at weekly intervals	500,000,000				
Then at weekly intervals ...	550,000,000	Slight local reaction			
	600,000,000		12.5.33	A few pus cells	*B. coli*
	650,000,000				
25.5.33	Vaccine stopped				
			28.7.33	A very few pus cells	Sterile
			29.9.33	An occasional pus cell	Sterile

Tuberculous Epididymitis and Tuberculous Hydronephrosis.—HUGH LANKESTER, B.Ch. (by permission of W. T. GORDON PUGH, M.D.).

A. B., male, aged 16 years.

History.—August 1930: admitted to Princess Mary's Hospital, Margate, with acute tuberculosis of left hip. April 1932: the right epididymis was observed to be enlarged. Tubercle bacilli found in urine. May 1932: transferred to Queen Mary's Hospital, Carshalton. *On admission.*—Painless hard swelling of both epididymes, right more swollen than left; not adherent to skin. Nodular thickening of right vas. Both testes and the left vas appeared to be normal. The kidneys were not palpable. Rectal examination: vesicles not enlarged. Wassermann reaction and Kahn test: negative. Urine: pus and blood cells present. The culture shows the presence of *B. coli*. Numerous tubercle bacilli are present, both in direct films and in an inoculated animal. Skiagram of renal tract: no abnormal shadows. Intravenous pyelography: no excretion from left kidney; right pelvis and ureter normal. Cystoscopy.—Bladder-wall normal except for œdematous left ureteric orifice; right orifice normal; no tubercles. Right ureter: catheter passed easily; left obstructed one inch up from orifice.

Urine from right ureter contained pus cells. The culture showed a growth of *Staphylococcus albus*. No tubercle bacilli found (direct or in inoculated animal).

Operations (performed by Mr. J. Everidge, F.R.C.S.).—August 1932: right and left epididymectomy, with excision of each vas up to internal ring. The testes appeared normal and were replaced.

September 1932: left nephrectomy. The kidney was a large thin-walled hydronephrotic sac with tubercles on surface. The ureter was the size of small intestine.

Pathological report on the left kidney.—(Summary.) "Chronic tuberculosis with extensive fibrous tissue formation."

Progress.—The boy made an uneventful recovery from all operations. He has been recumbent throughout for treatment of the hip. He has had a full course of tuberculin treatment.

Present condition.—Patient has gained 1 st. 3 lb. in weight in fourteen months. The testes appear normal. The left hip is quiescent. Urine: a few pus cells. No tubercle bacilli (direct or in inoculated animal). Blood urea: 17·8 mgm. per 100 c.c. Intravenous pyelography: dilatation of right renal pelvis and ureter.

Pyelonephritis with Renal Failure and ultimate Recovery. — T. S. RODGERS, M.D. (for K. H. TALLERMAN, M.D.).

R. G., female, aged 6 years, was admitted to the London Hospital on 5.4.33 with a history of eight days' headache, vomiting, drowsiness and oliguria. Three weeks before she had had earache, but otherwise had been well until this illness.

On examination.—She was a very ill-looking, pale, fat, drowsy child. Temperature 97·4°, pulse 86. The blood-pressure was 185/140 and there was a little œdema of the ankles. The heart, throat, ears and fundi were normal. The urine was red with blood, boiled almost solid, and on culture *B. coli* were grown, but there was no pus. The blood urea was 0·379%.

Progress.—In the first four days there were several fits (which were treated with lumbar puncture, venesection and intramuscular and rectal injections of 20% magnesium sulphate), and for the first two weeks the child remained drowsy and vomited at intervals. There was oliguria for the first week. At the end of the second week the temperature, which had risen slowly to 101°, fell to normal. The clinical condition improved and the urine became loaded with pus. A few days later her condition again became worse, her temperature rose and a tender swelling was felt in the right loin. Until the beginning of the sixth week she remained febrile (101°) and drowsy, and passed blood and sometimes pus in the urine. Her condition then rapidly improved, the vomiting ceased, her blood urea fell to 0·03% and her blood-pressure to about 120/80. She was discharged in the twelfth week looking well, and her urine appeared normal apart from a trace of albumin.

16.11.33: She has remained well since discharge, and on examination there are no physical signs, but her urine still contains a trace of albumin.

Investigations:—

Blood urea.—	5.4.33	0·379%	1.5.33	0·064%	
	8.4.33	0·444%	16.5.33	0·03%	
Urea excretion.—	16.5.33	1st hour	75 c.c.	0·54%	
		2nd hour	75 c.c.	0·6%	
Urea concentration test.—	22.5.33	2nd hour	8 c.c.	1·2%	
		3rd hour	44 c.c.	1·5%	
	14.6.33	3rd hour	44 c.c.	2·8%	

X-ray examination.—21.4.33: Showed no evidence of calculi in either kidney. Kidney shadows well seen and appeared big, especially the right. (Dr. Vilvandré.)

Oral pyelography attempted, but unsuccessful.

Pyelogram.—16.11.33 : Left side appears to be normal. Right side: double ureter ; some dilatation below junction. (Mr. V. W. Dix.)

Cerebrospinal fluid normal. 5.4.33.

Wilms' Tumour, or Renal Embryoma of Infancy.—DONALD BATEMAN, L.R.C.P., M.R.C.S. (for DONALD PATERSON, M.D.).

M. S., female, aged 2 years.

Complaint.—Recurrent attacks of dark discoloration of urine.

Family history.—Only child. No consanguinity between the patients.

History.—In April, June, August and October 1933 the patient had attacks of dark discoloration of the urine. Each attack cleared up in about two weeks. During the August attack the patient was feverish and irritable. The patient was again feverish and irritable during the October attack. She was admitted to Westminster Hospital on 19.10.33. There was some pain during the August and October attacks. She was gaining weight.

State on admission.—A pale, somewhat apathetic child. A large mass was present in the right kidney region. The mass was hard, with uneven surface, not adherent to skin, slightly movable, and painless. Urine : Contained albumin, many pus cells, and no blood. During the previous attacks the urine had not been examined, but was described as having looked like " weak or strong tea." Blood urea : 30 mgm. %. Radiographic reports : 20.10.33 : No evidence of pulmonary disease. 21.10.33 : Following uroselectan injection, left kidney normal. Right shows no filling—suggestive of sarcoma.

Operation.—24.10.33 : The right kidney and the large tumour involving it were removed by Mr. G. T. Mullally. The growth was infiltrating the inferior vena cava.

Pathological report on the growth.—A tumour expanding the upper pole of the kidney ; the specimen measures 6 in. by 5 in. It is lobulated and involves the renal vein. On its upper pole the suprarenal is expanded : and in the growth in this area there is a laminated clot, due histologically to an organizing hæmorrhage into the growth. Microscopically there is a typical rhabdomyosarcoma (congenital renal teratoma of Wilm). It consists chiefly of small round cells, but typical areas of myxomatous and epithelial tissue are present.

Progress.—A transfusion was carried out before the operation. A good recovery was made, and the child was discharged 6.11.33.

Sexual Precocity in a Girl aged 3 Years.—M. BOLTON, L.R.C.P., M.R.C.S. (for ALICE KING, M.D.).

M. M., aged 3 years, was brought to the Queen's Hospital for Children in September 1933, with a minor ailment. Her precocity being commented on, the mother stated that the child grew pubic hair at the age of 1 year and in the following two years the breasts developed and she grew rapidly in height.

Menstruation apparently commenced three weeks after the first attendance. The child complained of abdominal pain and was miserable during one day. The mother discovered a blood-stained vaginal discharge which had completely ceased when the child came to hospital the following day.

On examination.—Mental development : difficult to assess. She is extremely self-conscious and has no idea how to play with other children, but her intelligence is at any rate not subnormal for her age. She speaks infrequently while in hospital, but is said to like adult company at home.

Physical condition : Good. The child is fat, with breasts well developed, and numerous pubic hairs. The facial expression is heavy. Since admission to hospital the temperature has swung between 98° and 103° F. Examination of the central

nervous system shows nothing abnormal, and palpation of the abdomen under an anæsthetic also revealed nothing abnormal.

Height: 41 in. Weight: 2st. 13 lb. Blood Wassermann reaction, negative. Blood-calcium: 11·3 mgm. per cent. Blood-phosphorus: 4·4 mgm. per cent.

Blood-sugar curve:	(1) Fasting	0·122%
	(2) ½ hour after taking glucose ...	0·198%
	(3) 1 „ „ „ „ ...	0·158%
	(4) 1½ hours „ „ „ „ ...	0·132%
	(5) 2 „ „ „ „ ...	0·112%

White cell count: 19,200 per c.mm. (Taken when temperature was 103°.)

Urinary test for pituitary dysfunction: negative.

Skiagrams.—Skull, nothing abnormal. Long bones: development of carpal bones and epiphyses very advanced for her age.

Dr. J. D. ROLLESTON wondered whether, in view of the case of adrenal sexual precocity in a boy aged 4 years 11 months, recently reported by Player and Lisser,[1] it would not be advisable to carry out pyelography in order to detect the presence of an adrenal tumour. In Player and Lisser's case a tumour was found by pyelography on the upper pole of the left kidney and was excised. The boy was alive and well twenty months after the operation, and showed considerable modification of his endocrine abnormalities. According to the writers this was the first example of a successful operation for this condition.

Report on Case and Specimen of Double Ureterocœle with Dilated Ureters and Early Hydronephrosis.—T. S. KEITH, M.B., and S. A. OWEN, M.D.

M. F. G., male, born 20.9.33, died 5.10.33.

History of patient.—Six weeks premature. Admitted on second day of life for prematurity. Took his feeds well, but did not thrive. No urinary dysfunction noted.

Post-mortem examination.—Corpse was minute, and slightly jaundiced; abdomen distended. Head: Not examined. Thorax: Terminal bronchopneumonia, otherwise nothing abnormal. Abdomen: Liver fatty, with cloudy swelling; stomach and intestines dilated to region of splenic flexure, then empty and contracted. Other abdominal organs, except kidneys, etc., were normal.

Specimen.—Kidneys, ureters, and bladder.

The kidneys are normal in size, and show fœtal lobulation. One kidney has been bisected and shows a slight dilatation of the renal pelvis.

The ureters are considerably distended, but there is no kinking, and no abnormal vessels were present.

The bladder is very thick-walled. On either side external to the ureteric orifices (through which bristles have been passed) are two plum-coloured folds, like polypi. These are free except at their bases, and were sufficiently long to obstruct the orifice of the posterior urethra. The posterior urethra (which is laid open) appears to be normal.

Congenital Heart-block.—T. S. RODGERS, M.D. (for A. MAITLAND-JONES, M.D.).

M. E., female, aged 10 years, "has always been short-winded," so her mother says, and sometimes "goes blue" on exertion. There is nothing else of importance in the history.

On examination.—A moderately well-nourished child. No cyanosis or clubbing of the fingers. Heart enlarged; apex beat forcible; in fourth space in midclavicular line; some dullness to right of sternum. There is a harsh, systolic murmur over the whole

1 *Urol. and Cut. Rev.*, 1933, xxxvii, 758.

precordium, loudest at the pulmonary area. The pulse-rate is regular at about 46, and on exertion (touching the toes twenty times while standing) it is little increased in rate. On one occasion numerous ventricular extrasystoles were noted. The blood-pressure is 145/100. Normal pulsation could be felt in the femoral arteries, and there is no evidence of an anastomotic circulation either clinically or in the skiagram of the chest.

There are no other abnormal physical signs, and no other congenital abnormalities have been noted.

Orthodiagram (13.11.33).—Heart enlarged: left ventricle enlarged, right auricle enlarged. Pulmonary artery and conus only slightly enlarged.

Electrocardiogram, leads I, II and III. Complete heart-block.

(Oblique I, barium) Aorta slightly enlarged to right, but knuckle is to left of the barium stream. Lung roots clear (Dr. J. C. Hoyle).

Electrocardiogram.—Complete heart-block. Ventricular rate 40, auricular rate 80. No special preponderance (Dr. J. C. Hoyle).

The literature records 44 cases of congenital heart-block, 35 being cases of complete block; in 26 cases a patent septum had been diagnosed. In most of these 44 cases there were few symptoms referable to the heart. In the five autopsies recorded all the cases showed septal defects.

Three Views of Parts removed from an Infant, the subject of several Deformities.—J. B. MACALPINE, F.R.C.S.

1. (*Centre*) *Posterior aspect.*—Note below, a rosette with a central depression where the rectum opened into the posterior urethra.

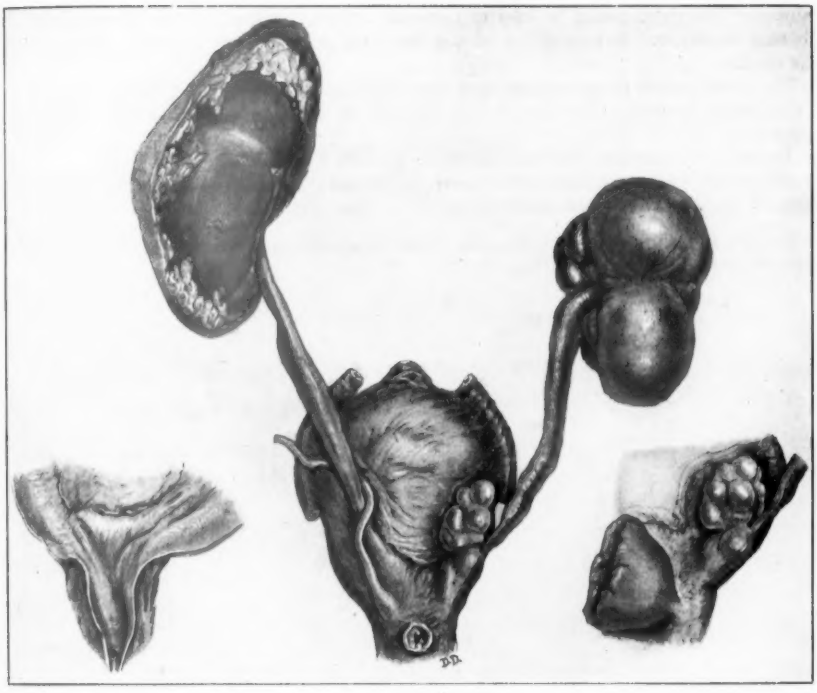
The right ureter opens into the right seminal vesicle which is dilated. The corresponding kidney is hydronephrotic and cystic.

There was no vas deferens on this side.

The left ureter and vas deferens are inserted normally. The vesicula seminalis of this side is not visible. (? accidentally removed.)

2. *Anterior view.*—Asymmetrical trigone showing normal insertion of the left ureter and an undeveloped right ala. The dimple in the posterior urethra is the opening of the rectum.

3. *Lateral view.*—Before removal of funnel of rectum, showing attachment of this to the prostate, etc.



(2) (1) (3)

Parts removed from an infant, the subject of several deformities. Specimen (lent by Mr. E. D. MacCrea) shown by Mr. J. B. Macalpine.

Atrophy of the Testis following Neonatal Orchitis (? Intra-uterine Torsion).—T. HOUSTON, M.B., Ch.B. (for HELEN MACKAY, M.D.).

G. M., a Jewish boy, aged 17 months, born 18.6.32.

Pregnancy and delivery were normal; it was a head presentation. The mother's Wassermann reaction was negative. She had one other child, said to be healthy.

Condition at birth.—Weight 7 lb. 10 oz. A "hard lump in the scrotum" was noted by the midwife as soon as the child was delivered. The left testis was greatly enlarged, about the size of a pigeon's egg, firm and slightly tender. The cord was thickened; the scrotal skin was not red, or involved in any way. On the right side there was a small hydrocele, with an apparently normal testis. The child was normal in all other respects, and there were no constitutional symptoms.

Subsequent history.—At 7 weeks old the left cord was still thickened. The left testis diminished in size fairly rapidly, and when the baby was 2½ months old was only slightly larger, though considerably harder, than the right. At 7 months of age it was the size of a small pea, and very hard; at 10 months of age no testis could be felt in the left side of the scrotum. At 16½ months of age a small hard testis was thought to be felt in the groin, but subsequent examination has not confirmed this.

Present condition.—A well-nourished child. Examination of the various other

systems fails to reveal any abnormalities. He has been circumcised (ritual circumcision). The right testis is in the scrotum and is normal. The left side of the scrotum is empty. Invagination of the left inguinal canal gives the impression that it is empty.

The commonest cause of neonatal orchitis is presumed to be intra-uterine torsion of the testes or cord. Torsion of the hydatid of Morgagni has been recorded as a cause.

In one case orchitis was secondary to umbilical infection.

In several cases, operation has been performed; and nothing abnormal except the signs of torsion, have been discovered.

Dr. HELEN MACKAY described a case of bilateral neonatal orchitis which had proceeded, as in this case, to atrophy.

Section of Otology

President—W. J. HARRISON, M.B.

[*December* 1, 1933]

Simplified Method of Determining Percentage of Actual Hearing-power in Tuning-fork Tests

By Sir JAMES DUNDAS-GRANT, K.B.E., M.D., F.R.C.S.

THE first step in calibrating a tuning-fork is to determine its rate of decrement and for our purpose the number of seconds required for its amplitude to diminish by one-half. In a previous paper [1] I described a method of observing directly the decrement in amplitude by means of the microscope, for forks ranging from 16 to 1,024 cycles per second. I find it can also be done by a comparatively simple optical method.

A small concave mirror (as used for galvanometers) is fixed on the outer side of one blade of the tuning-fork close to the tip, and a counter-weight on the other. The fork is fixed in a firm vice and a light is directed on to it from a spot-light or, if more convenient, from the otologist's own bull's-eye lamp, unfrosted and fitted with a metal or cardboard diaphragm with a central perforation $\frac{1}{2}$ mm. in diameter. The light is directed on to the mirror and from it is reflected, as a luminous dot, on to a sheet of cardboard. When the fork is set in vibration the dot changes into a vertical line (fig. 1 and fig. 2*a*) which shortens more or less rapidly, the time required for it to shorten from any length to half that length being ascertained by means of a stop-watch. On the cardboard are ruled two diverging lines and these are joined by vertical lines, say $\frac{1}{8}$, $\frac{1}{4}$, $\frac{1}{2}$, and 1 in. in length. The board is placed so that the vertical line of light is over one of the longer lines, say the one measuring 1 in. (fig. 2*b*); then the stop-watch is started, and when the line is reduced to $\frac{1}{2}$ in. exactly (measuring by the centre of the rounded "knob" at each end) the board having been moved along until the bright line falls on the $\frac{1}{2}$ in. line, the stop-watch is stopped and the "half-amplitude" time is ascertained (fig. 2*c*). Larger amplitudes should be avoided as the law of isochronous vibration applies only to small ones. It is well to repeat the process several times and take the average, using, when possible, different lines (say 1 in. to $\frac{1}{2}$ in. and $\frac{1}{2}$ in. to $\frac{1}{4}$ in.).

For the highest pitched forks, 2048 and 4096, another method is available. The observer stands with his ear at say six feet from the vibrating fork and then slides towards it, keeping the loudness at the same degree till he is three feet from it. The number of seconds required for this gives the half-amplitude-time, as described in my former paper.

[1] *Journ. Laryng. and Otol.*, 1929, xliv, 380.

Having got by experiment the half-amplitude-time, divide by it the number 1·386 (*a*). Subtract the quotient (*b*) from 4·605 (*c*) and the remainder gives us the *number corresponding* (*d*) to a *deficit of 1 second* in the table below, from which can be read the percentage of audition.

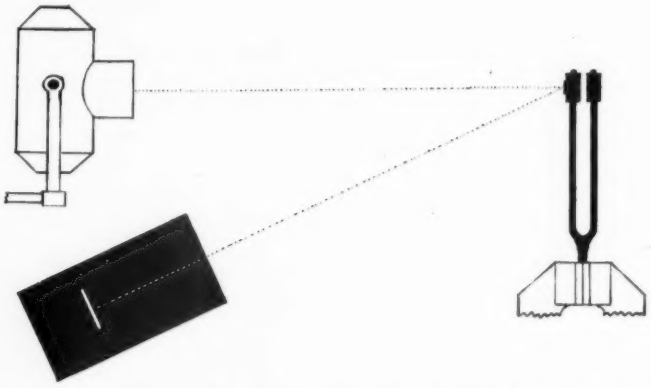


FIG. 1.—Lamp, vibrating fork with concave mirror and reflection of light on to scale.

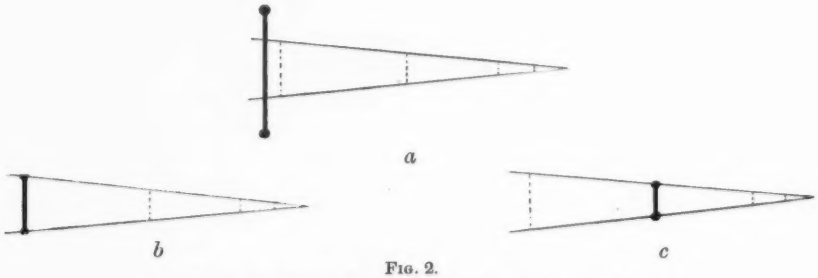


FIG. 2.

a.—Vertical luminous line before start of counting seconds.
b.—The same when starting the count.
c.—The same when stopping the count, i.e. at half-amplitude.

Subtract a second time the same figure from the remainder and we get the *number corresponding* to the percentage for a deficit of 2 seconds, Subtract a third time and we get the same for 3 seconds, and so forth.

TABLE OF NUMBERS CORRESPONDING TO PERCENTAGE OF AUDITION.

Number	Percentage	Number	Percentage	Number	Percentage
4·605	100	4·174	65	3·401	30
4·554	95	4·094	60	3·218	25
4·500	90	4·007	55	2·995	20
4·442	85	3·911	50	2·708	15
4·382	80	3·808	45	2·303	10
4·318	75	3·688	40	1·609	5
4·248	70	3·555	35	0·693	2

Example :—

Suppose a fork (c^2 = 512 d.v.) with a half-amplitude-time of 2·3 seconds :—

2·3) 1·386 (0·6026 (i.e. 1·386 divided by 2·3 gives a quotient of 0·602

1·38

60

46

140

138

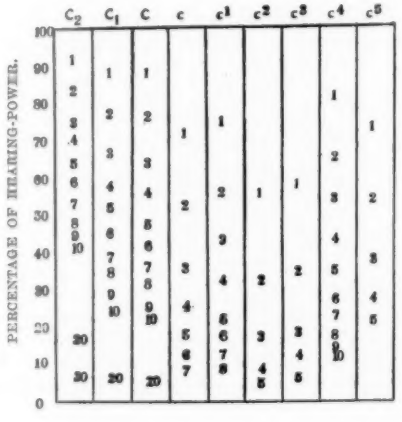
	From 4·605		
	Subtract 0·602		
Deficit of 1 second	4·003	corresponds to	55%
	0·602		
Deficit of 2 seconds	3·401	,, ,,	30%
	0·602		
Deficit of 3 seconds	2·799	,, ,,	16%
	0·602		
Deficit of 4 seconds	2·197	,, ,,	9%
	0·602		
Deficit of 5 seconds	1·595	,, ,,	5%
	0·602		
Deficit of 6 seconds	0·993	,, ,,	3%
	0·602		
Deficit of 7 seconds	0·391	,, ,,	1·5%

In a blank chart with vertical columns graduated for percentages, one for each fork, mark the figure 1 (one second) in the column for c^2 at the level of 55%, figure 2 at that for 30% and so on.

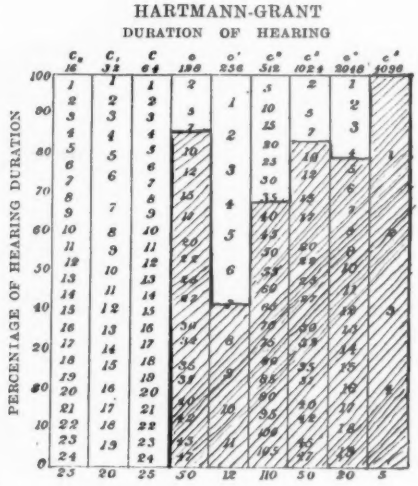
To obtain the percentage of "hearing-power" for that fork we have, therefore, only to put a mark on the figure of the deficit of "hearing-audition" in seconds.

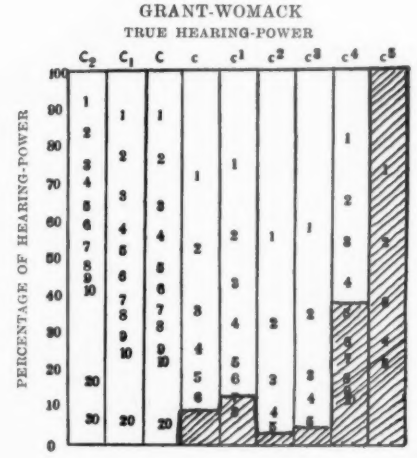
For other forks the same process is carried out and their columns graduated in the same way.

For the set of forks which I use, the blank chart is numbered as below :—



To illustrate the practical use of this chart the second of the two below shows the true percentage of hearing-power arrived at as above described in an actual case, while the first gives the erroneous results obtained by charting merely the shortage in duration of hearing for the forks.





A chart devised by my secretary, Miss Dickson, can be prepared with very much less calculation, as in the accompanying table. In the first column is given the fraction or multiple of half-amplitude-time of the fork ("H.A.T."), and in the second the corresponding percentage of hearing-power (all percentages being given to the nearest whole number). Thus, deficit to the extent of the half-amplitude-time is equivalent

to 25 per cent. of the hearing-power; to the extent of one quarter of the half-amplitude-time, it is equivalent to 71 per cent. hearing-power, and so on:—

⅛	"H.A.T."	... ...	83-84%
¼	"H.A.T."	... ...	71%
½	"H.A.T."	... ...	50%
	"*H.A.T.*"	... ...	25%
1½	"H.A.T."	... ...	12-13%
2	"H.A.T."	... ...	6%
2½	"H.A.T."	... ...	3%
3	"H.A.T."	... ...	2%
3½	"H.A.T."	... ...	1%

Other numbers can be interpolated without any considerable degree of error.

The figures in the chart below refer to my set of forks, but can be used for any forks which have the same half-amplitude-times.

PERCENTAGE OF HEARING-POWER	C_2	C_1	C	c	c^1	c^2	c^3	c^4	c^5	
83	2	1·2	1	0·5	0·6	0·2	0·3	0·8	0·5	⅛ "H.A.T."
71	4	2·5	2·2	1	1·2	0·5	0·6	1·6	1	¼ "H.A.T."
50	7·5	5	4·5	2	2·4	1	1·2	3·2	2	½ "H.A.T."
25	15	10	9	4	4·7	2·3	2·5	6·5	4·4	"*H.A.T.*"
12	22	15	13	6	7	3	3·7	9·7	6·6	1½ "H.A.T."
6	30	20	18	8	9	4·6	5	13	8·8	2 "H.A.T."
3	37·5	25	22·5	10	11·4	5·7	6·2	16	11	2½ "H.A.T."
"H.A.T."	15″	10″	5″	4″	4·7″	2·3″	2·5″	6·5″	4·4″	

NOTES.

(*a*) The number 1·386 is obtained from the equation:—

$$a = a_0 e^{-\frac{1}{2}kt}$$

a being the amplitude at the end of time t in seconds and a_0 the original amplitude, k the constant peculiar to the particular fork.

Then a being one-half of a_0

$$\tfrac{1}{2}a_0 = a_0 e^{-\frac{1}{2}kt}$$

and dividing each side by a_0

$$\tfrac{1}{2} = e^{-\ kt}$$

that is to say, $-\frac{1}{2}kt$ is the Naperian log. of $\frac{1}{2}$ which is $-0{\cdot}693$; then

$$-0{\cdot}693 = -\tfrac{1}{2}kt; \text{ and } kt = 0{\cdot}693 \times 2 = 1{\cdot}386$$

k is therefore $\frac{1{\cdot}386}{t}$, i.e. 1·386 divided by the half-amplitude-time.

(It may be noted that if the energy decays according to $E = E_0 e^{-kt}$ Amplitude decays $a = a_0 e^{-\frac{1}{2}k}$ since Energy is proportional to the square of the amplitude.)

(*b*) The "quotient" is k, the constant peculiar to each fork depending on the particular structure as regards material, size, weight, formation, etc., in which forks may differ, as to rate of decrement, from each other, although of the same pitch.

(*c*) 4·605 is the Naperian logarithm of 100.

(*d*) The "number corresponding" is the Naperian logarithm of the percentage of audition for the deficit in seconds T of duration of hearing in accordance with the equation:—

$$\frac{\text{Hearing-power } A \text{ of patient}}{\text{Normal (100 per cent.) } B} = e^{-kT}$$

(Vide *Journ. of Laryngology*, June, 1929, vol. xliv, p. 388.)

$$\text{Log}_e \text{ patient's hearing} - \text{Log}_e 100 = -kT$$

$$\text{Log}_e \text{ patient's hearing} - 4{\cdot}605 = -kT$$

$$\text{Log}_e \text{ patient's hearing} = 4{\cdot}605 - kT$$

If T is one second, then it is $4{\cdot}605 - k$

If T is two seconds, then it is $4{\cdot}605 - 2k$

If T is three seconds, then it is $4{\cdot}605 - 3k$

Hearing Aids and Hearing Tests

By C. S. HALLPIKE, F.R.C.S.

ALTHOUGH the story of otology within the last thirty years has been in some ways a story of success—success in the treatment of gross infective processes of the middle ear tract and their complications—there must be few otologists who need to be reminded of their limitations when confronted with the average case of non-suppurative deafness.

The otoscopic view is limited by the drum. Certain classical exercises with tuning forks may lead to some such information as Rinne −15, Schwabach +3, which, however academically interesting, has a negligible importance compared with the information already supplied by the patient that he is compelled to say "what?" some fifty times a day. When the question of relieving this state of affairs arises, the patient is told that hearing aids exist, and is encouraged to consult one or another dealer where an aid may be selected, more or less at random, to suit his taste.

There must be few otologists, if I may be allowed one more gloomy platitude, who have not regretted this somewhat ignoble state of affairs, and in introducing this subject for your discussion, I do not intend to engage you with technical details of apparatus, which, indeed, I am incompetent to do, but rather to try to deal with the questions:

Should it not be possible for otologists, by some objective assessment of the ear's function comparable to refractions in the eye, to predict with satisfactory accuracy the type of hearing aid required?

Secondly, to what extent are hearing aids ever likely to remedy hearing defects with the same precision that spectacles remedy most visual defects?

Now in the eye the method employed of investigating most visual defects is an analytical examination of the eye's anatomy, the cornea, vitreous and retina being

in turn systematically assessed. In the ear this is impossible. Although abnormalities of the tympanic membrane may be observed, most otologists will agree that cause for wonder occurs not only that patients with certain observed imperfections of the membrane are deaf, but also that patients with as great or greater imperfections can hear so well. The same surely applies too often to the evidence supplied by that other classical exercise, inflation by a Eustachian catheter.

In the ear, then, the method of anatomical analysis is virtually impossible, and our chief hope, therefore, must lie in an analysis of function. What, firstly, is there to analyse? The patient's complaint is of inability to understand speech, or in other words, a falling off of the ear's overall efficiency.

Now, speech itself, although a complex phenomenon, can be analysed with some facility and is found to be a medley of sound waves of frequency, varying from 100 ~ to 6,000 ~ per second, and there is good evidence for saying that the ability to understand speech depends upon the sensitivity of the ear for pure tones being unimpaired, certain ranges of tone sensitivity, as for example 500 ~ to 2,000 ~, being of greater relative importance than others. Granted that this is the case, also the possibility of testing accurately the hearing for pure tones, we should be able in this way to give at any rate one reason why speech is not heard properly.

The question which at once arises is whether such an audiogram in a case of deafness really gets us any further. Are we not merely proving by the aid of a diagram that the reason the patient is deaf is that he cannot hear? in other words expressing function in terms of function? and the answer is categorically, Yes. But such I submit are the only terms in which at present one can truthfully describe many cases of deafness. What one hopes to be able to do is to describe deafness in terms of anatomy. I may well be reminded here that the Bezold tradition, upon which are based most of the functional tests used by otologists to-day, does purport to describe deafness in terms of anatomy, and I am as aware as anyone of the futility of disturbing long-established tradition, the more so as one may regard the Bezold tradition to be well founded upon facts. That is to say that the clearest cut cases of conducting deafness, as stapes ankylosis, give the Bezold triad, whereas in the clearest cut cases of nerve deafness, as in senile deafness, the reactions are entirely distinct. Satisfactory as are these clear-cut types, it is, I think, a matter of common enough experience that many cases of advanced chronic deafness occur in which Bezold's tests give very mixed results, and these cases are described usually as being cases of mixed deafness. Here, I fear, the limits of legitimate inference are passed.

For this reason: That increased fixation of the conducting mechanism which is the physical basis of the Bezold triad is not of necessity the only possible result of middle-ear affection. Other types of distortion in the direction of undue laxity, may often occur in which case the Bezold triad, if considered as an index of middle ear disease, would give negative results. The deafness in such cases must, it is often inferred by exclusion, be of the inner-ear type, or partly so. Actually the condition may be just as purely middle-ear in anatomical character as a stapes ankylosis. So far then as the Bezold triad goes, cases of deafness can only be given an anatomical basis with any satisfaction in a limited class of middle-ear disease, namely, stapes ankylosis. For a large proportion of cases of chronic deafness it will require a good deal more systematic investigation of temporal bones of accurately tested cases of deafness, before otologists can feel justified in describing these cases in fundamental terms of anatomy. In the meanwhile I cannot help thinking that otologists would be wiser to consider deafness more in terms of functional tests, and of the functional tests at our disposal the most important is the so-called pure tone audiogram.

Two considerations support this statement. Firstly, that the pure tone audiogram bears a fairly constant and intelligible and often illuminating relationship to the

overall performance of the ear in dealing with speech. Secondly, that it forms a promising basis from which some accuracy and intelligence in the construction and prescription of hearing aids may be expected to arise. As regards the co-relation of hearing for speech and pure tones, we have to realize *a priori* that there exist important differences between the experimental conditions which obtain during pure tone tests and listening to ordinary conversation. In listening to pure tones the stimulus is more or less prolonged and the time factor negligible.

In listening to speech a rapid succession of sound waves fall upon the ear and are not repeated, being either heard or not heard once and for all. The time of action of the stimulus would, it may be thought, be of considerable importance. This has to do with what physiologists call the chronaxie or time strength relationship of a stimulus.

Few who have used tuning-forks for quantitative tests can, I think, have failed to notice apparent discrepancies which sometimes occur between the results of such tests and the deafness to speech. Thus most often a marked loss for speech may be present with comparatively small loss for the tuning-forks. It occurs, I think, most often with nervous adults who are anxious not to be found deaf. I believe it to be chiefly due to one of the inherent defects of tuning-fork tests, namely, that

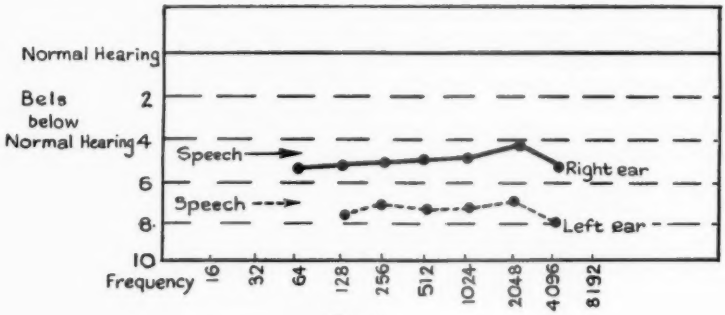


FIG. 1.

the stimulus applied is one of the dying-away variety. Workers upon threshold values with senses other than the auditory find that errors of this type are very prone to occur when the stimulus applied is of the dying-away type, and may assume large proportions.

It is important to employ stimulation rising from sub-threshold values.

Though the value of pure tone tests is open to some question, it is only fair to add that the amount of precise evidence that such factors as chronaxie period play an important part in deafness is at present small. Moreover, the published results of workers who have employed well-controlled audiometric methods longest justify the view that significant indiscrepancies between pure tone and speech tests do not occur.

I should like to show on the screen a reproduction typical of results published in Harvey Fletcher's book, in which voice tests are recorded along with the pure tone audiogram (fig. 1).

On the whole it is justifiable to say that valuable insight into overall hearing loss for speech is provided by accurate pure tone audiograms. And that although there exist other factors, such as the chronaxie disturbance which still needs investigation, the pure tone audiogram still remains the most valuable piece of information at our disposal.

The remaining question is, how audiograms can be employed as a basis for the construction of hearing aids.

An easily understood method is to construct receiving circuits with or without amplifying valves, which have a resonance corresponding to the frequency band of the deafness. The late Mr. Wharrie introduced a method of using carbon microphones of varying degrees of hardness which had resonances in different parts of the scale. By using one or the other or a combination of these carbons, a microphone could be produced with a resonance corresponding more or less to the area of deafness.

Mr. Wharrie's published work shows that good results were obtainable by this method. The difficulty is, of course, the accurate fitting of the resonances of the instrument to the areas of hearing loss. If, as may be, there is a generalized loss with a small relative dip at 4,096, a carbon arrangement with a sharp peak at 4,000 will give a painful intensity at 4,000 before the neighbouring frequencies are brought up to the threshold, and so one type of distortion will be replaced by another.

Another factor which deserves consideration in the aiding of hearing is the varying effect of extraneous noise in different types of deafness. Here it may not be inapt to recall the truism that the ear does not enjoy the facility of the eye in being able to devote itself to one thing at a time. Senile types of deafness are often much disturbed by traffic noise or conversation. They are often best helped by such an apparatus as a speaking tube, which tends to exclude all but the speaker's voice.

Left FIG. 2. Right

The use of hearing aids employing bone conduction is naturally a subject of interest, owing to the large numbers of cases of deafness with comparatively good bone conduction.

The results obtained are actually often disappointing, owing possibly to the distortion resulting from varying hand pressure of the instrument upon the skull. A more primitive type of such device is the so-called acoustic fan.

I wish finally to say a few words upon the interesting but obscure subject of artificial drums. It is generally stated that in cases of gross defect of the tympanic membrane, such a device as a loose pledget of cotton-wool introduced into the ear in a manner not very well defined, will sometimes result in marked improvement of hearing.

A few years ago it was discovered by two American investigators, Wever and Bray, that when sound waves fell upon an intact living ear of the mammalian type electrical oscillations are set up in the ear with a frequency corresponding to that of the sound. These oscillations can be picked up by suitable electrodes and after amplification can be heard upon a loud speaker, speech itself being in this way well reproduced.

In the course of investigating this phenomenon, Hughson and Crowe of Baltimore found that the strength of the oscillations was increased by inserting a small cotton-wool plug into the niche of the round window pressing upon the secondary tympanic membrane. Hughson and Crowe considered the strength of these oscillations to be a probable index of the animal's hearing, and argued that pressure upon the round window membrane was a method of improving hearing.

I do not propose here to go into the question of what precisely this Wever and Bray phenomenon has to do with hearing beyond assuring you that the circumstantial evidence that it has a good deal is now considerable. But I should like to show you a piece of film dealing with this matter taken in the course of some investigations of the Wever and Bray effect now in progress at the Ferens Institute (fig. 2).

In this experiment is employed a cat lightly anæsthetized with nembutal with a platinum electrode in the neighbourhood of its exposed internal ear, an indifferent electrode being placed in the muscles of the neck. The impulses picked up by the electrodes are passed through a valve amplifier and thence on to an oscillograph which traces out the amplitude and form of the electrical waves upon a piece of moving film. Into the cat's ear is passing a sound of constant intensity and of a frequency of 500 cycles per second. A small cotton-wool plug is laid in the round window niche with a fine silk thread attached by which it can be instantaneously removed.

On the left of the film can be seen the oscillations with the plug in place. The line A represents a small lamp, which is turned off at the moment of withdrawing the plug. This occurs at the point X and following the disturbance due to the withdrawal of the plug the oscillations are seen to be re-established, but are now much reduced in amplitude.

The note of inquiry which I wish to introduce concerns the possible clinical bearing of these facts. That occlusion of the round window niche may improve hearing in the human is not unknown to clinicians. Bárány's writings upon the subject are dealt with by Schaefer and Giesswein writing in Denker and Kahler's Textbook. My first personal experience of it was as Mr. Mollison's house surgeon in being encouraged to drop small beads of mercury into the niche through large perforations.

Is it at all an established principle among clinicians that success in the use of so-called "artificial drums" depends upon pressure upon the round window membrane in accordance with the facts just described?

The Use of the Audiometer

By G. P. Crowden, M.Sc., M.R.C.S., L.R.C.P.

(*Lecturer in Industrial Physiology, London School of Hygiene and Tropical Medicine*)

The problems of deafness and minor impairment of the function of hearing may be studied from the points of view of clinical medicine, otology, education or national health, and it is from this last standpoint, namely that of preventive medicine, that I wish to present to you the findings of investigations with the gramophone audiometer in this country during the past four years.

In May 1929, I made inquiries at the Central London Recruiting Depot, Whitehall, as to the tests and standards of physical fitness employed by the Army, and was not a little surprised to learn from the Senior Medical Officer that the main cause of rejection of men for the Army on medical grounds was old and current middle-ear disease. Such men are unfit for service in the Army, for experience has shown that they are particularly liable to break down under the strain of training—a strain which every young man should be fit enough not only to stand, but to profit by.

Out of 49,182 men medically examined for the Army in 1927 [1], 13,536 or 30·2% were rejected as physically unfit mainly for the reasons shown in Table I.

While 41·38 per thousand were rejected for disease of the middle ear in 1926-27, the Reports on the Health of the Army for 1930 and 1931 show an even greater rate of rejection of recruits for this condition and deafness than for previous years, the actual figures being 51·69 in 1930, and 53·97 per 1,000 examined in 1931. Moreover,

in both years more than five men per thousand who passed the medical officer in the first instance were discharged on account of middle ear disease within six months of enlistment, this being the major cause of subsequent discharge from the Army during training.

TABLE I.—CAUSES OF REJECTION OF MEN FOR THE ARMY, 1926-27.

Condition	Ratio per 1,000 rejected on examination
Disease of middle ear	41·38
Loss or decay of many teeth	36·78
Defects of the lower extremities	34·73
Defective vision	28·51
Other diseases of the heart...	24·93
Insufficient weight	17·28
Valvular disease of the heart	16·86
Flat feet	13·40

It is apparent from these Army returns that middle-ear disease and other pathological conditions associated with deafness are major causes of physical disability in the nation, and that any means leading to the detection of such conditions at stages when there is a reasonable chance of cure has a distinct bearing on national health.

The obvious question to be asked when figures such as these are published is, "Did the condition of disease arise before, during or after school age?" and such considerations led to an investigation being initiated and carried out by the London School of Hygiene and Tropical Medicine in 1929-30, into the methods of detecting and the incidence and causes of minor degrees of deafness in school children. The tests were carried out on elementary school children in the Borough of Hornsey with the consent of the Medical Officer of Health, Dr. R. P. Garrow and the Education Authorities [2]. The 4A Gramophone Audiometer (Fig. 1), developed by the Bell

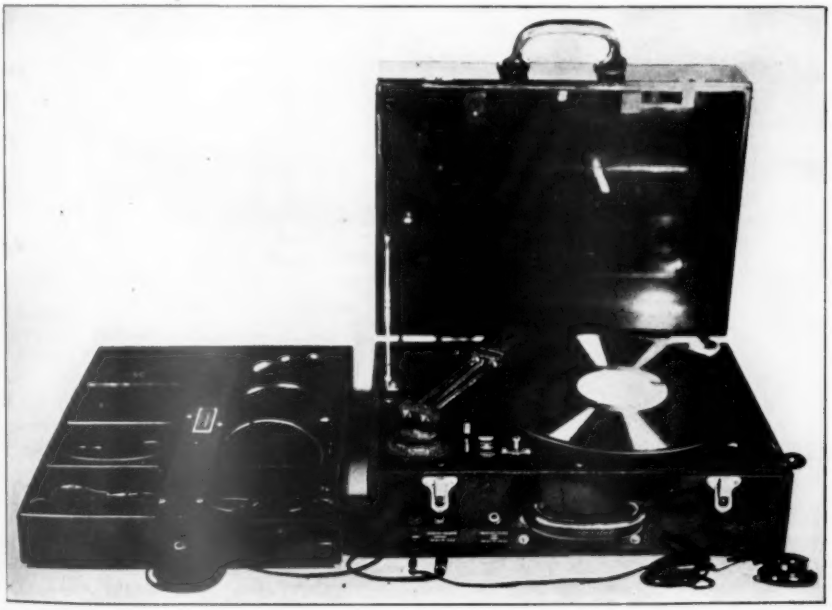


FIG. 1.—The gramophone audiometer.

Telephone Research Laboratories in New York, was used and it proved to be a good and ready means of rapidly testing the hearing of children for speech sounds, and for picking out those with minor degrees of deafness. In this preliminary investigation 1,483 children, ranging in age from 8 to 15 years, were examined, and it was found that 6·6% showed evidence of impaired hearing in one or both ears [3]. After an interval of six months the routine testing was continued in the same locality, but in different schools, and similar results were obtained. The results of the investigations in Hornsey are shown graphically in Fig. 2. In all 2,608 children (1,368 boys and 1,240 girls) were tested, the percentage failing the test being 6·8. Further tests in an L.C.C. school and an entirely independent investigation in the Borough

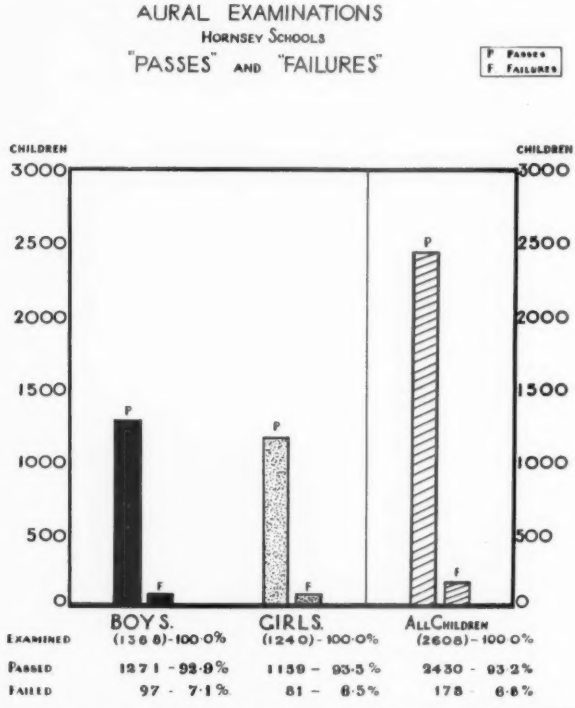


FIG. 2.—Results of audiometer tests in Hornsey Elementary Schools, 1929-30.

of Tottenham support the finding that from 6 to 8% of children of school age have some impairment of hearing in one or both ears at the present time. Fig. 3 shows the combined results of the audiometer tests on 6,898 children (3,292 boys and 3,606 girls).

The returns for the routine medical inspection of school children given in the Annual Reports of the Chief Medical Officer of the Board of Education have, for some years past, recorded the incidence of defects of hearing as slightly less than 0·5%, and it is worthy of note that the Board of Education recorded the fact that: "Deterioration of hearing may go on for some time before it is noticed" (vide "Handbook of Suggestions on Health Education," 1928, p. 52). Of necessity, cases

of defective hearing must first be detected before curative measures can be directed at the underlying cause, and in the past the failure in detection of early signs of deafness has been due to the lack of suitable and reliable physiological tests and methods of assessing the hearing of school children in a reasonable period of time.

Audiometer tests.—With the gramophone audiometer it is easily possible to test 400 children in a day. Each ear is tested separately, and from 1 to 40 children can be tested at a time, as the record played on the audiometer is relayed to forty separate head telephones, all of which, owing to the wiring system, deliver sounds of equal intensity to the ear. There is obviously no opportunity for lip-reading, while, by the use of numbers which the children are asked to write down on the forms provided, any spelling difficulty is avoided, and the fact that most children

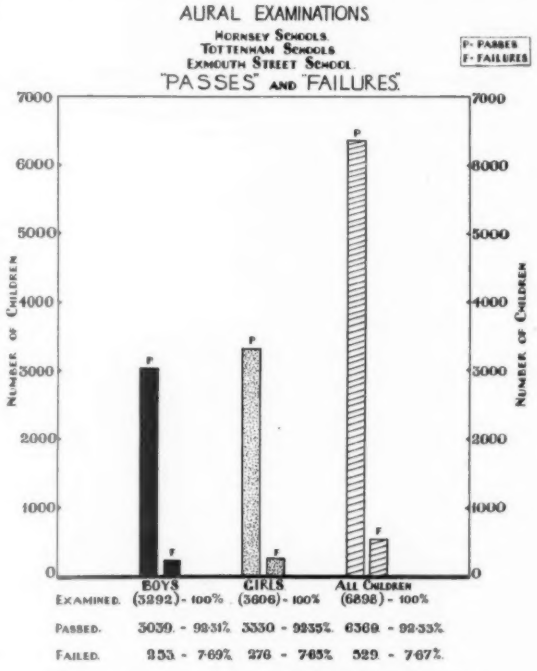


Fig. 3.—Results of audiometer tests in three localities.

have listened to wireless sets makes it an easy matter to gain their interest and co-operation in the test. Fig. 4 shows a form filled in by one child who had a minor loss of hearing in the right ear.

The gramophone record consists of groups of numbers of three or two digits, each figure of which is spoken, and each succeeding group of digits is at a lower intensity corresponding to a three decibel drop in loudness. In the making of the record the voice was kept as uniform as possible, the steps down in loudness being achieved by the electrical recording apparatus now employed for cutting the original wax record from which the copies are made for use.

In the test, the child listens and writes down the numbers so long as he can hear them, and the level of failure indicates the level of loudness above the normal

threshold or zero base line at which he can just hear speech sounds. In other words, he has lost hearing for speech sounds at levels between zero and the point where he recorded the numbers correctly, the difference being his hearing loss in sensation units or decibels. Roughly speaking, each step down of three decibels corresponds to a reduction in intensity by a half.

In elementary schools with group testing, approximately 10% of the children fail the first time they do the test, i.e. they fail to record numbers correctly below the level of 9 units on the scale (see Fig. 4). All the children who fail the test in one or both ears are retested within a day or two, and the names of those who fail a second time are submitted to the medical officer for medical examination and treatment. The second test eliminates a few children who fail the first test through nervousness, lack of attention, or temporary indisposition such as acute colds, which are often attended with impairment of hearing sufficient to prevent the very weak speech sounds at the lower levels being heard.

NAME *b J*
AGE *12*
STANDARD *Form 1.*
DATE *Oct 21 · 10 · 1930*

DO NOT MAKE ANY NOISE AS IT WILL SPOIL THE TEST

INSTRUCTIONS

YOU WILL HEAR NUMBERS SPOKEN BY A PERSON WHO IS MOVING AWAY FROM YOU THE VOICE WILL GET WEAKER AND WEAKER LISTEN CAREFULLY AND WRITE AS MANY NUMBERS AS YOU CAN

HEARING LOSS	RIGHT EAR 1	2	3	4	LEFT EAR 5	6	7	8	HEARING LOSS
30	526	538	863	646	526	538	863	646	30
27	348	363	234	662	348	363	234	662	27
24	414	318	546	648	414	918	546	648	24
21	111	868	288	624	111	868	288	624	21
18	648	388	883	381	648	338	883	331	18
15	526	162	416	462	526	182	416	462	15
12	826	148	813	462	826	548	813	452	12
9		351			363	351	345	168	9
6					528	241	588	831	6
3					634	586	133	833	3
0					124	566	413	596	0
−3					853	134	165	335	−3
	HEARING LOSS 9				HEARING LOSS − 3				

FIG. 4.—Test form used with gramophone audiometer.

Improvements in the manufacture of gramophone records and the advances which have been made in telephone engineering have made it possible to standardize gramophone audiometers and headphones so that variations from set to set are negligible, and to ensure that each ear piece or headphone transmits frequencies over a range covered by ordinary speech whether the voice be male or female. The apparatus is as durable as any good gramophone. There are no batteries to keep up or replace, for the pick-up is a magnetic one of special construction and power. Each record can be used 100 times without material deterioration, so that upwards of 2,000 children may be tested per record, the record being played twice for each group of 40 children, i.e. for the right and left ears respectively.

Routine use of the audiometer.—One audiometer and a set of 32 headphones is adequate for a school population of some 25,000 children as proved by the experience of the Borough of Tottenham, where an instrument has been used systematically for the past two years.

The systematic use of the gramophone audiometer as an aid in attacking the problem of impaired hearing in both its educational and medical aspects may be outlined in stages as follows:—

(i) Detection of cases and measurement of defects by audiometer tests.
(ii) Medical examination and diagnosis.
(iii) Medical or surgical treatment.
(iv) Re-testing each case by audiometer to assess effect of treatment.
(v) Decision by medical and educational authorities in regard to the subsequent care of the child.

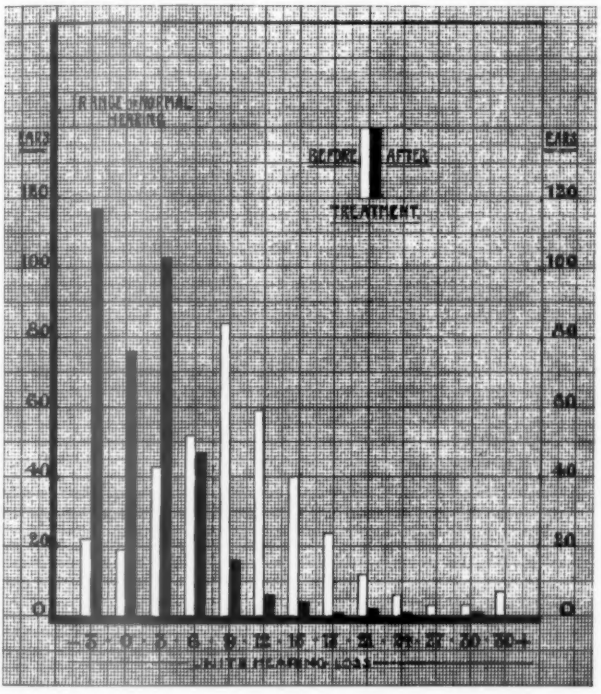


FIG. 5.—Results of audiometer tests before and after treatment. Tottenham schools.

This routine was suggested in 1931 [4] and has since been adopted and proved to be practicable in the Borough of Tottenham. The names of all the children who fail the test are submitted to the school medical officer and passed on to the aural specialist who arranges for them to attend the weekly clinic. After a period of time the children who have been examined and treated are re-tested by the audiometer and the results of the treatment assessed. Figs. 5 and 6 reproduced from Dr. A. R. Friel's report in the Annual Report of the School Medical Officer, Tottenham, for the year 1932 [5], show the results of this systematic attack on defective hearing, and the report itself should be consulted for information in regard to the methods of treatment (notably "Diastolisation" devised by Dr. Gautier of Paris), which have been successfully employed to remedy the underlying pathological

conditions responsible for the impaired hearing in the children detected by the audiometer. A comparison of the white and black columns in these figures shows that complete restoration of normal hearing for speech resulted in a large proportion of the ears treated. It is worthy of note that in Fig. 5 cases of impaired hearing due to wax have been excluded.

Personnel required for school tests.—The use of the gramophone audiometer does not necessitate the presence of the school doctor or the aural specialist. In the first instance, in order to save a great deal of time and to ensure uniformity in method, it is desirable for someone conversant with the use of the apparatus for group testing in schools to test several groups of children as a demonstration to those who

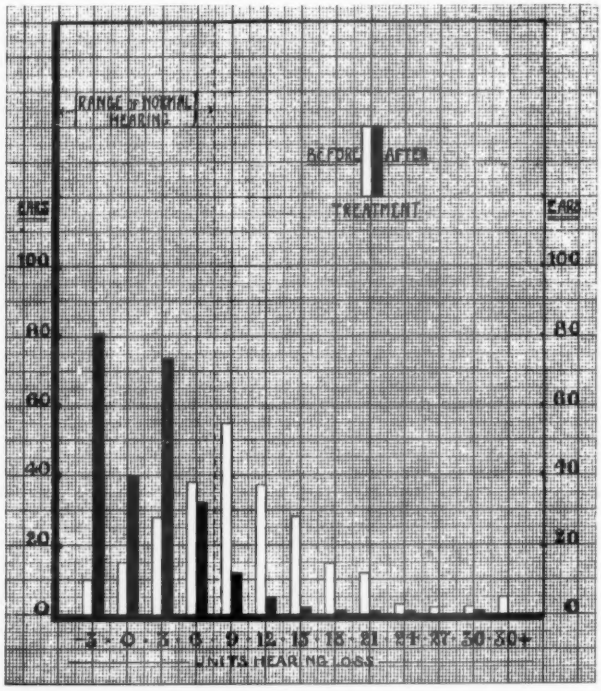


FIG. 6.—Results of tests before and after treatment; cases of defective hearing due to wax excluded. Tottenham schools.

will subsequently be responsible for carrying out the routine tests in the schools of the particular area. This was done in the case of Tottenham where the school clinic secretary, Mr. T. E. Cowan, and the school nurse have now systematically used the audiometer for the past two years, and tested upwards of 10,000 children in the elementary schools. The correction of the test sheets by key number cards is a straightforward matter but it is desirable that one individual should be responsible for this side of the work.

Hearing standards.—The normal range of hearing acuity for speech sounds as delivered to the ear by the audiometer is taken to be -3 to $+6$ decibels or sensation units, for it has been found in practice that whereas a hearing loss of 9 units can

usually be attributed to some abnormal condition, a hearing loss of 6 units is often present although no abnormality in the ear, nose or throat can be detected. This does not, of course, apply to every case, but for practical purposes there must be some agreed line of demarcation or physiological range of threshold acuity from which to assess the presence and degree of impaired hearing. While a hearing threshold of 6 units does not handicap the child educationally or in ordinary conversation, it is possible that in certain cases it is the beginning of some progressive decline in hearing acuity, and it may be worth while keeping such children under observation and re-testing them after an interval of a few months.

The results of the tests on children in the Borough of Hornsey have been carefully analysed in order to determine whether the physiological range of threshold hearing

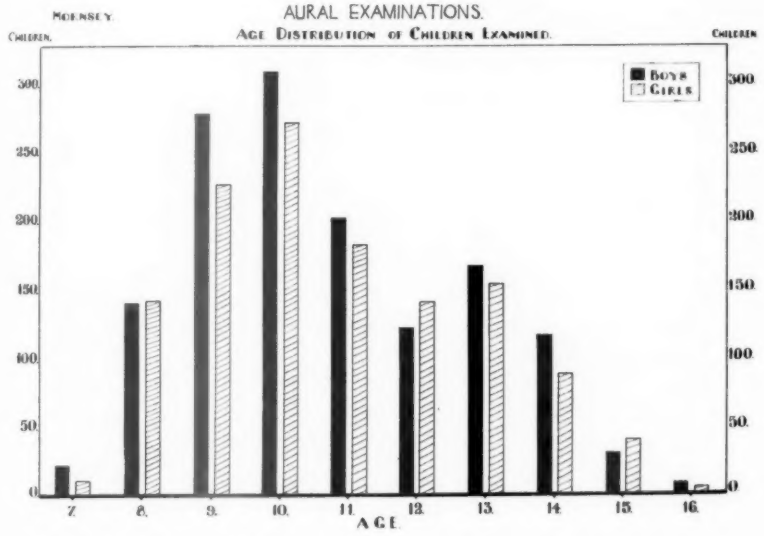


FIG. 7.—Age distribution of 2,608 children tested by audiometer. Hornsey, 1929-30.

acuity for speech sounds with the English record corresponded with the findings of American observers [6] on which the zero level or normal threshold acuity was based.

Fig. 7 gives the age distribution of the 2,608 children tested with the audiometer using the three-digit English record and the charts in Fig. 8 for 1,368 boys, Fig. 9 for 1,240 girls, and Fig. 10 for all the children show that an analysis of the hearing acuity levels of these children according to their better or worse ears reveals the fact that the mean threshold acuity for either group falls well within the arbitrary range of − 3 to 6 units. Moreover, the mean of the threshold acuity for the better and worse ears at each age is in the region of the zero or normal threshold level of loudness of speech sounds transmitted to the ear when the English speech record is used.

It appears, therefore, justifiable to use the zero level of loudness of speech sounds as the standard mean normal threshold from which to assess degrees of hearing loss or abnormal acuity of hearing in terms of definite decibel steps or units above or below this basic level.

Fig. 11 shows the percentage distribution of the ears of the boys and girls grouped according to their threshold hearing acuity or hearing loss, and it will be noted from this figure and from Figs. 8 and 9, that no material difference in the hearing of boys and girls was detected.

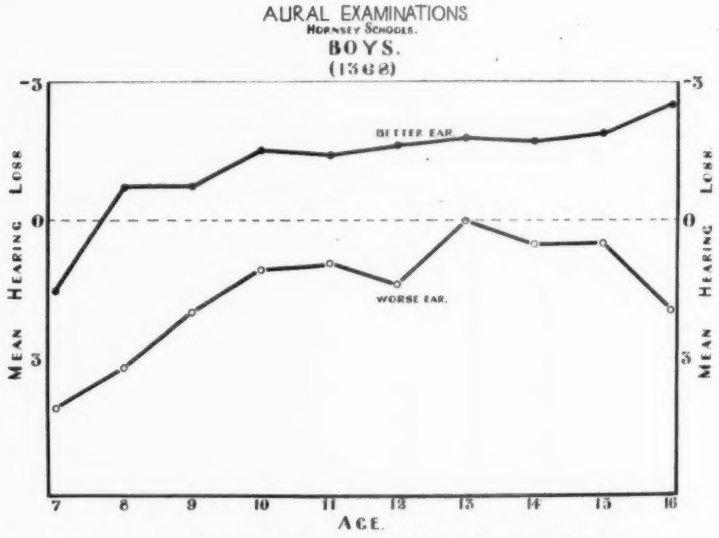


FIG. 8.—Mean threshold of acuity. Boys. Hornsey, 1929-30.

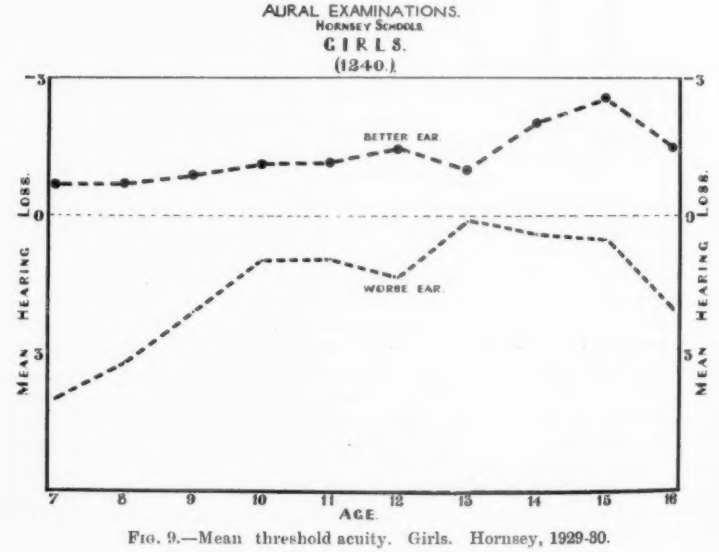


FIG. 9.—Mean threshold acuity. Girls. Hornsey, 1929-30.

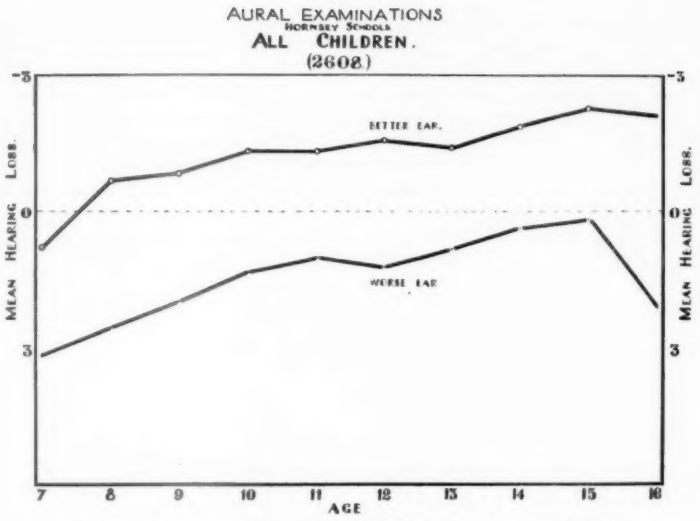


FIG. 10.—Mean threshold acuity. 2,608 children. Hornsey, 1929-30.

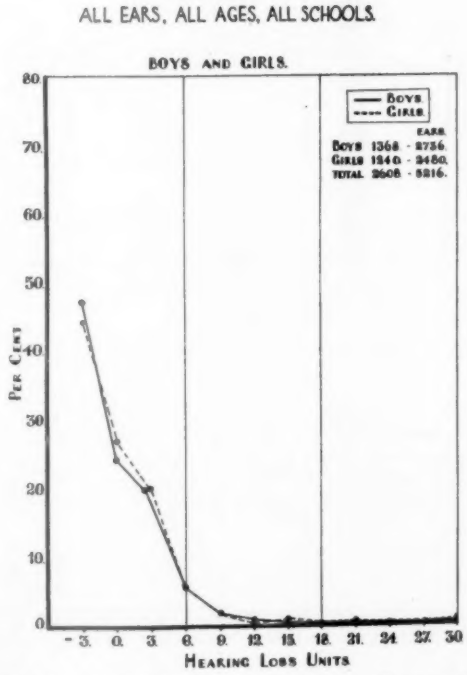


FIG. 11.—Acuity of hearing. Boys and girls, Hornsey, 1929-30.

Educational considerations.—In Fig. 12 the data of the tests in Hornsey are presented in different form, in order to show the distribution of defects according to degree of hearing loss. The percentages given are in relation to the number of ears tested, and therefore differ from the incidence of impaired hearing per 100 children.

Out of 5,216 ears tested, 5,020 or 96·28% were within the normal hearing threshold range of − 3 to 6 units, 156 ears or 2·97% showed a loss of 9 to 18 units, and 40 ears or 0·75% had a more severe degree of impairment of 21 to 30 units.

From the point of view of the need for medical attention, the total number of defects and number of children affected are significant, but from the educational point of view it is the hearing acuity of the better ear of the child which is of particular

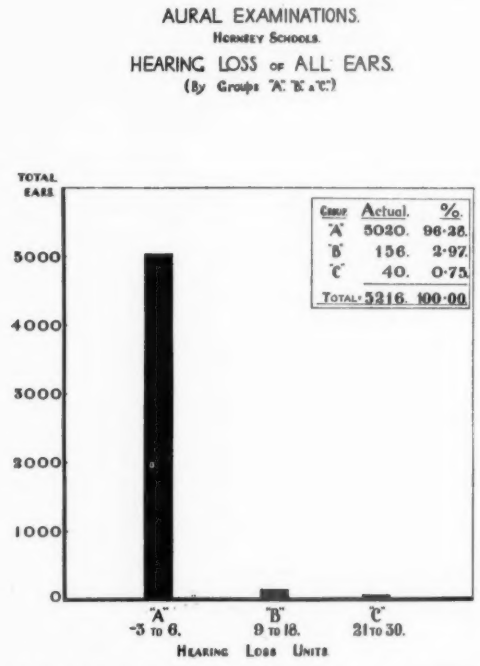


FIG. 12.—Hearing acuity of all ears tested. Hornsey, 1929-30.

importance; for while the health of the child may be seriously affected by pathological conditions giving rise to deafness in one ear only, the education of the child may not be materially handicapped, provided the hearing in the better ear is good. For this reason the better and worse ears of the boys and girls have been grouped separately in Fig. 13 and classified according to the degree of hearing loss as follows:—

Group A	Normal hearing	− 3 to 6 units threshold acuity
Group B	Minor impairment	9 to 18 units hearing loss
Group C	Partially deaf	21 to 30 units hearing loss

It will be seen from Fig. 13 that only one boy and two girls out of 2,608 children tested had a hearing loss in the better ear falling within the range 21 to 30 units.

While Group B children, with a hearing loss of 9 to 18 units in the better ear, may not be seriously handicapped in school work (although they should be given a good place in the classroom), the children in Group C would certainly find difficulty in hearing their teachers, for many children with this degree of deafness are already in schools for the hard of hearing. If this degree of deafness persists after treatment by the aural specialist, it is essential that such children should be taught lip-reading so that they can take advantage of the elementary school education.

A hearing loss in the better ear of 30 to 42 units would necessitate special educational care in a school for the hard of hearing unless improved aids for the deaf make it possible for such children to continue in the elementary schools. Such aids, however, would not obviate the necessity of teaching these children lip-reading,

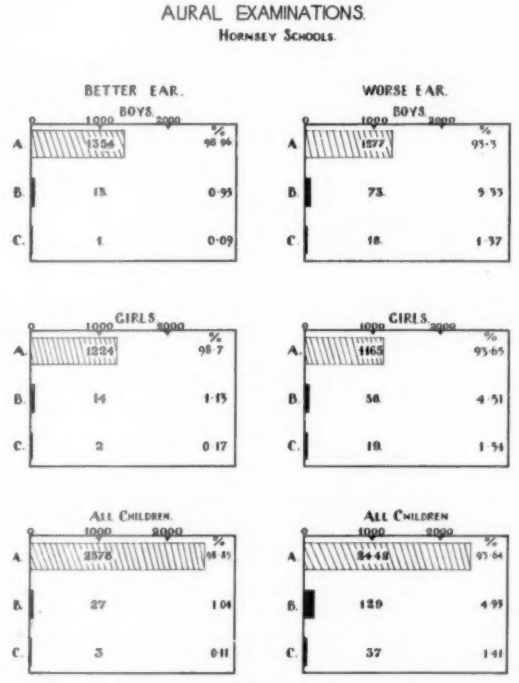


FIG. 13.—Hearing of Hornsey children in better and worse ears.

but they would materially help their educational progress and speech, as proved by tests which have been carried out in conjunction with Dr. A. G. Wells of the L.C.C.

The English-made gramophone audiometer, produced by the Western Electric Company, enables hearing to be tested for degrees of deafness up to 75 units loss and the children in the hard of hearing schools of the London County Council have been tested with the instrument. As shown in Fig. 14, the mean hearing loss of these children ranges between 30 and 42 units. Children in the special schools for the deaf have a still greater degree of loss and are sometimes difficult to test with speech sounds owing to the fact that many of them have not made use of what residual

hearing they still possess. It is, however, usually possible to test the hearing of these children with the pure tone audiometer.

Tests for children of pre-school age.—While the two or three digit number records are suitable for audiometer tests on children above the age of 7, these records cannot be used unless the child is able to write.

In view of the fact that the onset of deafness may occur at very early ages, and that the common diseases of childhood may be followed by conditions giving rise to impaired hearing, it is important to be able to detect minor impairment of function in children of pre-school age. With this end in view, a special record was made in 1931, consisting of simple words which could be pictorially represented. One of the teachers of very young deaf children was asked to furnish a list of words representing the earliest pictures of objects which are used in the teaching of such children. In collaboration with Mr. Stephen Jones of the Phonetics Department of University

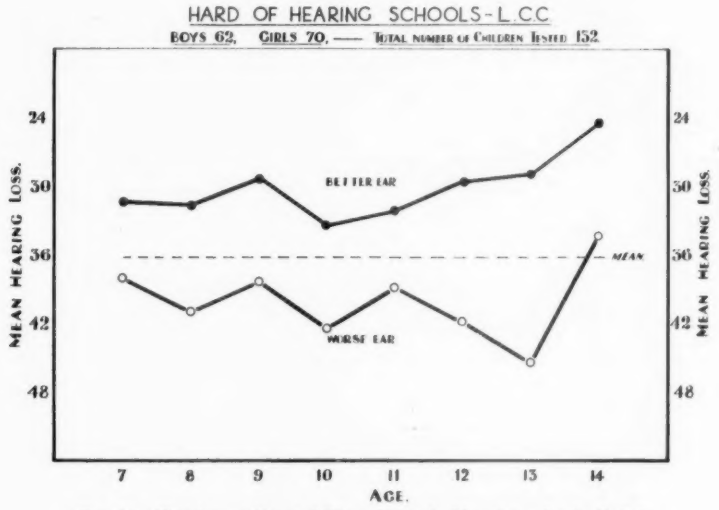


FIG. 14.—Hearing acuity of children in hard of hearing schools, L.C.C.

College, London, a series of words was selected from this list comprising sounds of high phonetic power, because if the child failed to hear these it would certainly fail to hear speech sounds of lower phonetic power.

Each succeeding group of words on the record is stepped down in definite degrees, and in the test the child is instructed to pick up the picture of each object when it hears the name called through the headphone. The successful choice of the pictures determines whether or not the child has heard the sounds at each intensity, this giving a gauge of its hearing threshold. Children of the age of $5\frac{1}{2}$ have been successfully tested by this method, and recently Mr. T. E. Cowan, school clinic secretary at Tottenham, has further improved the test by devising a model containing shutters on which the pictures named in the record are painted. The child is asked to push down each picture as the name is called, and children of $4\frac{1}{2}$ readily co-operate in the test as it is particularly attractive. It is hoped that with an even simpler record, it will prove possible to test children younger still.

Conclusion.—It is apparent from the data obtained from the audiometer tests on children in the elementary schools in the Borough of Hornsey, and from the results

of the systematic use of the apparatus in other areas, that by means of this method attention is drawn to many cases of minor impairment of hearing and to the causative conditions which would ordinarily pass unnoticed by the child, the teacher, or the doctor, particularly if the hearing defect is unilateral.

It cannot be too strongly emphasized that impaired function is often one of the earliest signs of the onset of disease, and that the early detection of impaired hearing in children directs attention to the underlying cause at a stage when appropriate treatment stands a reasonable chance of proving successful.

If the systematic use of the audiometer were generally adopted in schools of every kind, and provision made for the special examination and treatment of the cases of impaired hearing detected, not only is it possible that the national and individual handicap of the widespread incidence of deafness would be lessened, but it is within the bounds of probability that the health of the nation would be materially improved.

My thanks are due to Dr. Kirkhope, Medical Officer of Health, Tottenham, for permission to publish the charts in Figs. 5 and 6, and to the medical and educational authorities of Hornsey, and the L.C.C., who have kindly given facilities and encouragement throughout the progress of the investigations now placed on record. I also wish to express my appreciation of the ready help which has been afforded by the Western Electric Company in bearing the expense of the production of the English speech records, to the Columbia Gramophone Company for gratuitously making the record for young children, to Mr. J. P. G. Dowman, F.S.S., for assistance in checking the data, and to Mr. W. R. Luxton for help in the school tests.

In the following bibliography references are given to official publications referring to the progress of the investigation at various stages, some of which are specifically mentioned in the text.

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3 *The Medical Officer*, 1930, p. 113.
4 *The Teacher of the Deaf*, 1931, p. 78.
5 *Annual Report M.O.H. and School Medical Officer, Tottenham*, 1932.
6 "Speech and hearing," Harvey Fletcher, 1929, Macmillan.
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8 *Annual Reports M.O.H. Tottenham*, 1930, 1931.
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[Dr. Crowden then gave a practical demonstration of audiometer tests.]

Discussion.

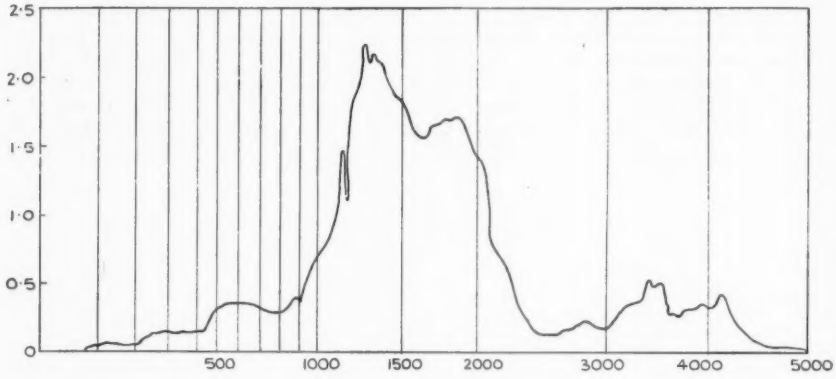
Mr. ALEXANDER TWEEDIE said that he had recently asked one of his friends engaged in the production of telephones to submit a critical report on the properties of electric aids. This report had been summarized in a "response curve" obtained from the best type of aid which his friend had inspected, and which he now showed (see figure, p. 40).

This, it would be seen, corresponded fairly accurately with that already shown by Dr. Crowden, and his friend had stated that other types in the market gave precisely similar curves.

The main point to be noted was that the peak of accentuation of sound fell between 1,000 and 2,500 D.V. per second, that is to say, was higher than what was usually regarded as the "speech area" (D.V. 128 to 512) which was only very slightly affected indeed. It was therefore this accentuation outside the "speech area" which probably represented one, at least, of the disturbing factors in these electric aids. The reason why electric aids did not offer the same help as the apparatus supplied in concert halls, his informant had stated, was that the microphone receivers there employed were of a different character.

Incidentally, his informant had also told him that the "aids" under inspection should be able to be manufactured wholesale at from say 28s. to 35s. each.

Anyone who was able to produce an electric aid which could definitely improve the range of hearing and that could be tolerated, would not only be welcomed with enthusiasm by the deaf, but also by all otologists, whilst at the same time no advertisement of such "aid" would be necessary and the name of the inventor would become immortal.



Input pressure approximately constant from 100-5,000 cycles/sec. to 18 dynes/sq. cm.

At the Nottingham Institute for the Deaf, in connexion with various annual fixtures, demonstrations of all available "aids" were held, the purpose of which was that the hard-of-hearing should have the opportunity of seeing all that was obtainable in that direction. In connexion with these demonstrations, the Institute issued the following pamphlet with the additional idea of preventing the deaf spending their money without sufficient opportunity of having tested the value of various "aids" before purchase:—

AIDS TO HEARING.

General Description.

These are all divisible into one of the two groups:—

(A) Some form of "Collector," an example of which is the well-known Ear Trumpet. (As a general proposition the larger the "Collector" the more useful the aid.)

(B) "Electric Appliances":—all based on the simple telephone, consisting of a microphone, telephone receiver and a small dry battery. (Amplifiers are sometimes associated with this type of apparatus, capable of producing a very great volume of sound, which may or may not be of assistance.)

Advice as to selection.

Collectors are more generally useful than "Electric" Aids, but are more conspicuous.

Electric Aids are sometimes successful.—Where amplifiers are added, they are too heavy to be portable. The batteries of course require renewal from time to time.

Three No's.

(1) NO person can decide as to the value of any "Aid" except the patient.

(2) NO "Aid" should ever be bought without the previous opportunity of two weeks' trial.

3) NO instrument maker should be trusted unless he will lend, on approval for two weeks, any "Aid" which the patient selects as possibly of use; with some reasonable arrangement for hire to cover wear and tear, risk of loss, etc.

The Secretary will be pleased to provide on request a list of Instrument Makers who will conform to the above methods of approval, trial and hire.

Dr. A. G. WELLS said it was only recently that regular audiometer work had been carried out among school children under the London County Council. Statistics would eventually be available on the subject, but could not be given yet.

There were points of interest which he had been able to note so far. One was that in the case of the bulk of the children who failed at tests 1 and 2 the fact of defective hearing had not been recorded on the medical record card, which was issued at the child's routine medical examination. Therefore ear defect which had been missed at the ordinary school clinic examination was revealed by the audiometer. A further important point was, that in those cases which had failed after the two tests and were examined clinically and treated, the failures were cut down greatly, in some groups of children by 50%. These facts showed the great value and utility of this instrument.

Many children were outside the ordinary range of hearing altogether, even with the loudest intensity of the adaptor. But on that there had hitherto been no regular work done, with the exception of that undertaken by Dr. Crowden.

Mr. A. J. M. WRIGHT referring to the work which he had done with the artificial drum, said he agreed, as a result of his observation, that in cases in which there was a considerable loss of tympanic membrane the apparatus acted in some way through its effect on the round window. But there were other cases in which the defect was relatively small, and then it would be found that the effect could be produced by closing the perforation by such a thing as a piece of moistened cigarette paper.

Mr. E. A. PETERS said the subject of artificial drums was a complicated one and probably depended on more than pressure on the lesser window. An artificial drum consisting of a pledget of wool soaked in glycerine or water was more efficient if the membrana tympani was absent. He had tried a dry plug of wool and found this of no avail.

Possibly the soaked plug and a bubble of air reconstituted the drum cavity or there was pressure on both windows.

Mr. TWEEDIE, referring to Mr. Hallpike's remarks on the action of the so-called "artificial drum," said he thought that this theory was really attributable to Bárány, who suggested that, normally, all sounds passed through the oval window and via the scala vestibuli, helicotrema, and scala tympani, out through the round window. This route was determined by the fact that normally mucus over the round window prevented vibrations travelling in the opposite direction.

In cases with a large defect of the tympanic membrane and a tolerant thus exposed middle ear, the application of some inert body like liquid paraffin, or mercury, in the round window, would represent the normal drop of mucus which in those cases was lacking. The effect of this method in such cases was of course well known, and he (Mr. Tweedie) reminded members that on a previous occasion he had told them of a patient who had found out the method himself, and was in the habit of shaping a little piece of bacon fat, and inserting it in the ear in order to improve his hearing.

Sir JAMES DUNDAS-GRANT asked whether pressure on the round window improved the hearing if the stapes was ankylosed. He hoped Mr. Hallpike would be able to fix the stapes in the Wever-Bray experiment and observe and report the result. It was understood that if both fenestræ were hermetically closed, hearing was practically abolished.

He had systematically tried to place an artificial drum on the exposed stapes, and most often with success. In a case in which an old inflammation had subsided it was difficult to know whether the stapes was mobile; if it was not, he thought an artificial drum placed on it was not likely to have an effect. But when the round window was exposed and the stapes ankylosed, there was no reason why hearing should not be carried on through the round window without any artificial drum; he had had cases which demonstrated that this was so. He had tried placing an artificial drum on the round window, and in one case at least it had caused severe vertigo.

Humanity had cause to be thankful for the introduction of the audiometer, and nothing would take its place for testing large numbers at a time. Bone-conduction could not be altogether eliminated, and could be carried through to the other ear when inequality of the

two sides existed. It was not necessary for every otologist to buy one of these instruments for his private practice. He believed that tuning-fork tests would always hold their own.

Dr. ALBERT A. GRAY said it was true that loss of hearing for low notes and a prolonged negative Rinne indicated obstruction in the sound-conducting apparatus, but they did not exclude affections of the nerve, as he (the speaker) had shown at the meeting of the Section in May 1933, in cases of otosclerosis with negative Rinne. In these cases the cochlear nerve was definitely affected, but the pathological changes were limited for the most part to the medullary sheath and neurilemma, the axis cylinder remaining normal in appearance.

Dr. CROWDEN (in reply) said the instrument which he had demonstrated was very unlikely to go wrong. That just seen had been in use for four years, and the record could be played 100 times, only fresh needles being required. The pure-tone audiometer could not be used satisfactorily in an ordinary room ; the room should be sound-proofed.

Mr. HALLPIKE (in reply) said that his reference to the Bezold triad meant that its absence did not necessarily mean the absence of a purely conducting deafness in the anatomical sense. Mr. Tweedie had pointed out that the carbon diaphragms of the type used by the late Mr. Wharry gave a response over the frequency range from 500~ to 2,000~, whereas speech frequencies were contained in the range below 500~. It was true that the energy of speech was mostly contained in the range below 500~, but it was generally agreed that the important range for the understanding of speech was that from 500 to 2,000, which in fact was the range dealt with by Mr. Wharry's carbon diaphragms.

Concerning the percentage method of expressing hearing losses for pure tones, described by Sir James Dundas-Grant, grave difficulties arose, since the ear's behaviour varied so greatly with frequency. Thus from 1,000~ to 2,000~ the ear was very sensitive while the intensity here could be increased over fantastic ranges before the practical upper limit of hearing, the pain threshold, was reached. Thus huge percentage losses might occur and still leave large reserves of hearing.

At the high and low ends of the scale the ear was much less sensitive, and the range of hearing restricted, the pain threshold soon being reached. Hence here comparatively slight percentage loss of hearing would result in complete deafness.

If the method of expressing hearing losses in percentages on the lines suggested by Sir James Dundas-Grant was adopted, the question would soon arise as to how it was that at this frequency (1,000~) a patient's hearing-power was reduced to 0·001% and yet he was able to hear a sound at that frequency of average conversational intensity quite well, while at 32~ his hearing-power was still some 90% and yet he was stone deaf to this frequency.

If the facts and implications of Wegel's fundamental sensitivity curves of the ear were more generally known, the question of expressing hearing losses in anything but decibels or half intensity units need never arise.

Sir JAMES DUNDAS-GRANT in further comment, said that he did not consider Mr. Hallpike's criticism applicable, as in the method described comparison was made with the hearing of a normal person, taken at 100 per cent. at all pitches. The conditions applying to the observed applied also to the observer and the comparison, therefore, held good. The results given in percentages of hearing-power were intelligible to everybody and were obtained in accordance with physical and mathematical requirements.

Two Cases of Paget's Disease with High Degree of Deafness, greatly helped by "Bone-Conducting" Electrical "Aid."—W. M. MOLLISON, M.Chir.

I.—W. H., aged 72. Complained of deafness of two years' standing. The results of tuning-fork tests are similar to those obtained in cases of otosclerosis. The head is large and for the last five years the patient has had to have hats made specially for him.

X-ray examination of the skull shows changes typical of Paget's disease.

One of the electrical aids that transmit vibrations to the bone by means of a special button helps the patient to hear much better than any other.

II.—(A more advanced case.) Elizabeth C., aged 68, has attended Guy's Hospital since 1916 on account of symptoms and signs of Paget's disease. The head is greatly enlarged and the tibiæ and femora are bowed. Deafness

was first complained of in 1921. There has been suppuration in both ears occasionally. A skiagram of the skull shows changes typical of the disease. (See figure).

The deafness is of high degree and similar in response to tests to that in the first case. With the "bone-conducting" electrical aid the patient can hear with comfort.

Tympanic Membranes which move with Respiration.—T. B. JOBSON, M.D.

E. E., male, aged 23, was referred to the Guildford Hospital on account of tinnitus of four weeks' duration. No history of previous ear trouble. (See figure.)

The right tympanic membrane is thin. It shows a striking in-and-out movement corresponding to inspiration and expiration. The left membrane moves a little with respiration but the excursion is much less than on the right. Both Eustachian tubes are patent.

Mr. E. A. PETERS said he had seen what appeared to be a similar case to this. Nasal obstruction was noticeable in the present case, and there was definite movement of the membrane even on light respirations. The drum was atrophic, the result of catarrh and patent Eustachian tubes.

Section of Therapeutics and Pharmacology.

President—J. H. BURN, M.D.

[*January* 9, 1934.]

Therapeutic Action of Injectio Ferri B P.

By G. N. BURGER, M.D. and L. J. WITTS, M.D.

ABSTRACT.—The injection of iron, which was introduced into the British Pharmacopœia, 1932, has been carefully tested in ten cases of anæmia.

The parenteral administration of iron is rarely desirable, because the therapeutic dose of iron by injection is so near to the toxic dose. Injectio Ferri B.P. has a very low therapeutic efficiency owing to its small content of iron; it is also painful, though this may be corrected by the addition of a local anæsthetic such as 3% procaine hydrochloride.

Double the maximum official dose of Injectio Ferri B.P., i.e. 14 mgm. of metallic iron, can apparently be safely given at one injection, but it would be necessary to give this dose twice a day for about six weeks to equal the effects of large doses of iron by mouth. The treatment of anæmia by weekly or bi-weekly injections of small doses of iron is irrational and to be deplored.

RÉSUMÉ.—L'injection de fer introduite dans la British Pharmacopœia, 1932, a été soigneusement expérimentée dans 10 cas d'anémie.

L'administration parentérale de fer est rarement à désirer, car la dose thérapeutique de fer injecté se rapproche de la dose toxique. L'efficacité de l'Injectio Ferri B.P. est très petite à cause de la petite quantité de fer qu'elle contient. L'injection est, d'ailleurs, douloureuse, mais on peut surmonter cet obstacle en ajoutant un anesthétique local tel que le chlorhydrate de procaine à 3 pour cent.

Il semble que deux fois la plus haute dose officielle de l'Injectio Ferri B.P., c'est-à-dire 14 mgm. de fer métallique, peut être injectée en une fois sans danger, mais il faudrait donner cette quantité deux fois par jour pour environ 6 semaines pour produire le même effet que les hautes doses de fer administrées par la bouche. Le traitement des anémies par l'injection de petites doses de fer une ou deux fois par semaine est irrationnel et à regretter.

ZUSAMMENFASSUNG.—Die in 1932 in die British Pharmacopoeia eingeführte Eisen-einspritzung wurde in 10 Fällen von Anämie sorgfältig nachgeprüft. Parenterale Eiseninjektionen sind selten erwünscht weil die therapeutische Dosis des injizierten Eisens sich der toxischen annähert. Die Heilwirkung der Injectio Ferri B.P. ist, wegen ihrem sehr niedrigen Eisengehalt, eine geringe. Die Einspritzung ist auch schmerzhaft, aber diesen Nachteil kann man durch Zusatz eines Lokalanästhetikums, z.B. 3 proz. Novocain, beseitigen.

Die doppelte offizielle Maximaldosis (das heisst 14 mgm. metallisches Eisen) scheint ungefährlich zu sein, aber diese Menge müsste man zweimal täglich für ungefähr 6 Wochen geben um dieselbe Wirkung als mit grossen peroralen Dosen zu erzielen. Die Behandlung der Anämie mit kleinen Mengen von Eisen ein oder zwei-mal in der Woche ist vernunftwidrig und nicht erwünscht.

To those of us who are interested in the treatment of anæmia, it was a surprise to find a preparation of iron for injection included in the last edition of the *British Pharmacopœia*, for there was little definite knowledge of the effects of the parenteral administration of iron in man until the experiments of Heath, Strauss and Castle, which were reported in November 1932, some months after the appearance of the Pharmacopœia. To judge by the discussion on the Pharmacopœia at the meeting of this Section held on December 13, 1932, the innovation was made "because there was a general feeling that injections of iron were of some use" (cited by Dorothy Hare). General impressions of this kind are often erroneous, and in our opinion the reputation of injections of iron is based on the treatment of patients who would have

recovered from their anæmia equally quickly without any treatment, and even more on the psychological effect of injections on patients with debility who were not anæmic. We have previously shown that the results of the treatment of chronic forms of anæmia, such as the idiopathic hypochromic anæmia of women, by the injection of iron have hitherto been very unsatisfactory, and in the present paper we hope to demonstrate that the Injectio Ferri B.P. is a relatively inefficient and impracticable preparation for ferrotherapy (Witts 1930).

From the study of anæmias produced in animals by iron deficiency or by repeated hæmorrhage, it has been concluded that the parenteral administration of iron is of no therapeutic value, and it has been suggested that iron is inactive in anæmia unless it enters the body by way of the alimentary tract and the portal circulation (Fontés and Thivolle). This is another example of the danger of transferring the conclusions of animal experiments to the spontaneous diseases of mankind, for the careful work of Heath, Strauss and Castle leaves no doubt that anæmia in human patients can be cured by the injection of iron. Such treatment is, however, fraught with difficulty, because the therapeutic dose of iron by injection is so close to the toxic dose. It is not generally realized how toxic injected iron is, though this has been clearly established in animal experiments (Starkenstein). That the results are applicable to man is apparent from the observations of Heath and co-workers :—

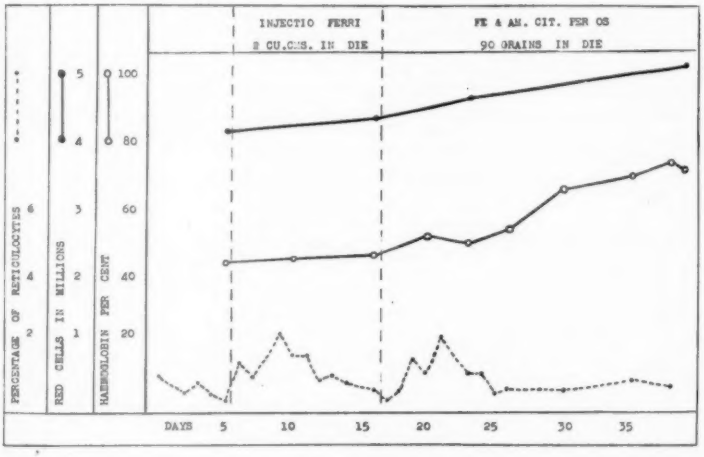
"Iron in doses of 16 to 32 mgm. a day, given parenterally, is very close to the maximum amount of iron tolerated by man. It is attended by disagreeable symptoms, sometimes severe and possibly dangerous . . . general warmth, palpitation and sometimes a pressure sensation in the region of the precordium, nausea and frequently vomiting. After the administration of 48 mgm. and 80 mgm. in two patients respectively, there were much more severe reactions . . . it was thought that such large doses of iron were distinctly dangerous."

Heath concluded that the effective dose of iron given by injection in the form of iron and ammonium citrate was 32 mgm. of metallic iron a day, and that this produced approximately the same effect as a daily dose of 1,000 mgm. of metallic iron given orally in the form of 90 gr. of iron and ammonium citrate. As already noted, toxic symptoms commonly follow the injection of 32 mgm. of iron, while larger amounts are distinctly dangerous. The maximum official dose of Injectio Ferri B.P. is 2 c.c., which contains 33 mgm. of iron and ammonium citrate or 7 mgm. of metallic iron. It may be noted in passing that few, if any, of the non-official preparations contain more of the metal than this. The official dosage is therefore a good deal less than the optimum determined by the American workers, so that we should hardly expect good results from its use. Indeed, Dr. Dorothy Hare has already reported a case in which 28 injections of Injectio Ferri B.P. were given to a patient in nineteen days without any improvement, though there was subsequently a good response to iron by mouth (Dorothy Hare).

In choosing the following ten cases for the evaluation of the therapeutic action of Injectio Ferri B.P., we have followed the criteria previously laid down, confining our attention to "cases which are of a torpid, chronic and constant type, which show no tendency to spontaneous recovery, and which are unlikely to be aggravated by uncontrollable factors" (Witts, 1933). Seven were women with idiopathic hypochromic anæmia; one was a case of gastric ulcer with hypochlorhydria, but without hæmorrhage; one case of toxic anæmia and one of carcinoma of the stomach were also included, in case such conditions should react better to the parenteral than the oral administration of iron. After an adequate control period Injectio Ferri B.P. was given intramuscularly daily for periods of from ten to twenty-one days; reticulocytes were estimated daily, hæmoglobin twice weekly and red cells weekly. For convenience the results have been expressed in diagrammatic form. In eight cases the daily dose of Injectio Ferri was 2 c.c., or 7 mgm. of metallic

iron; in two cases the daily dose was 4 c.c., or 14 mgm. of metallic iron; in no case were toxic symptoms observed. It was found an advantage to add 3% procaine hydrochloride to the injection of iron, as otherwise there might be much local pain. The injections were then omitted and replaced by the oral administration of iron, usually 90 gr. a day of iron and ammonium citrate, but in two cases 60 gr. a day of ferrous sulphate. The results were evaluated by the rate of increase of hæmoglobin during the two forms of therapy, and by the occurrence or not of a second reticulocyte crisis, for it is known that if a more powerful remedy is given when the reticulocyte crisis produced by a weaker remedy has subsided, a second reticulocyte crisis is usually induced.

I. *Idiopathic hypochromic anæmia with achlorhydria.*—Bertha M., aged 58, had suffered from dyspepsia and had been unable to eat meat for thirty years. For three years she had had glossitis, slight dysphagia, and anginal pain on exertion. She had complete achlorhydria with slight bleeding and absence of pepsin. Her blood-count was: red cells 4,110,000; white cells 7,200; Hb. 44%; C.I. 0·5. On eleven days' treatment with Injectio Ferri


INJECTIO FERRI
2 CU.CMS. IN DIE
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90 GRAINS IN DIE
PERCENTAGE OF RETICULOCYTES
RED CELLS IN MILLIONS
HAEMOGLOBIN PER CENT
DAYS 5 10 15 20 25 30 35

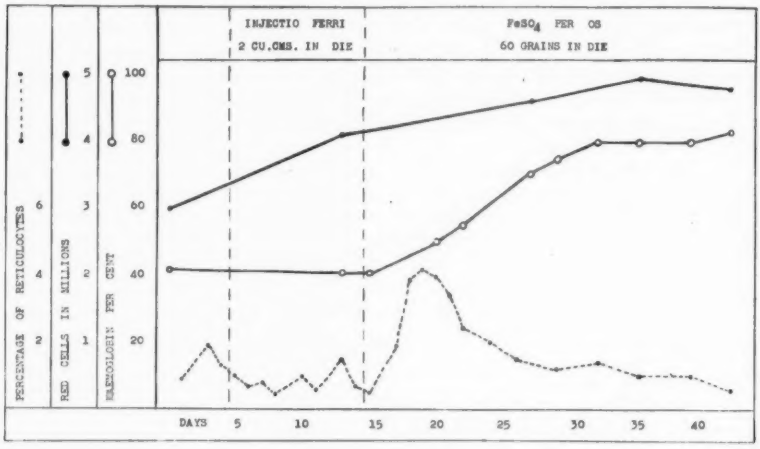
CASE 1. BERTHA M., 58, IDIOPATHIC HYPOCHROMIC ANAEMIA.

FIG. 1.

B.P., 2 c.c. daily, there was a small reticulocyte crisis with a peak of 2·2% and a rise of only 2% in the hæmoglobin. Treatment was then changed to iron and ammonium citrate, 90 gr. a day by mouth. There was a second reticulocyte crisis of equal height and the hæmoglobin increased from 46 to 72% in twenty-three days.

II. *Idiopathic hypochromic anæmia with normal gastric secretion.*—Olive M., aged 43, had had anæmia for over twenty years, the disease having been diagnosed as chlorosis at the onset. The diet was satisfactory, menstruation was scanty, the gastric secretion was normal, and apart from anæmia and slight dental sepsis there were no physical signs of disease and no obvious cause for the anæmia. Her blood-count was: red cells 3,020,000; white cells 5,100; Hb. 41%; C.I. 0·7. Injectio Ferri B.P. was injected intramuscularly, 2 c.c. daily for ten days; there was no reticulocyte crisis and no increase in hæmoglobin. She was then given ferrous sulphate, 60 gr. a day by mouth, when there was a reticulocyte crisis with a peak of 4·1% and the hæmoglobin rose from 40 to 83% in twenty-eight days.

III. *Idiopathic hypochromic anæmia with achlorhydria.*—Fanny R., aged 41, had been anæmic since girlhood, but had been worse for the last few months. She had complete achylia, confirmed by histamine; there was a mild proctitis, but no definite hæmorrhoids. She also complained of pains in the hips, though X-rays showed no disease of the bones. All


INJECTIO FERRI
2 CU.CMS. IN DIE
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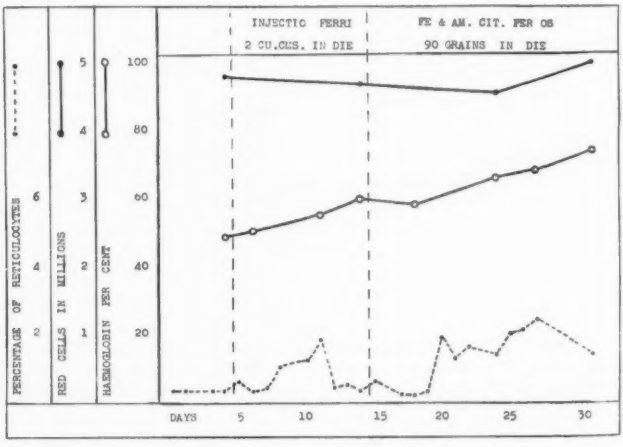
60 GRAINS IN DIE
PERCENTAGE OF RETICULOCYTES
RED CELLS IN MILLIONS
HAEMOGLOBIN PER CENT
DAYS 5 10 15 20 25 30 35 40

CASE 2. OLIVE M., 43. IDIOPATHIC HYPOCHROMIC ANAEMIA.

FIG. 2.

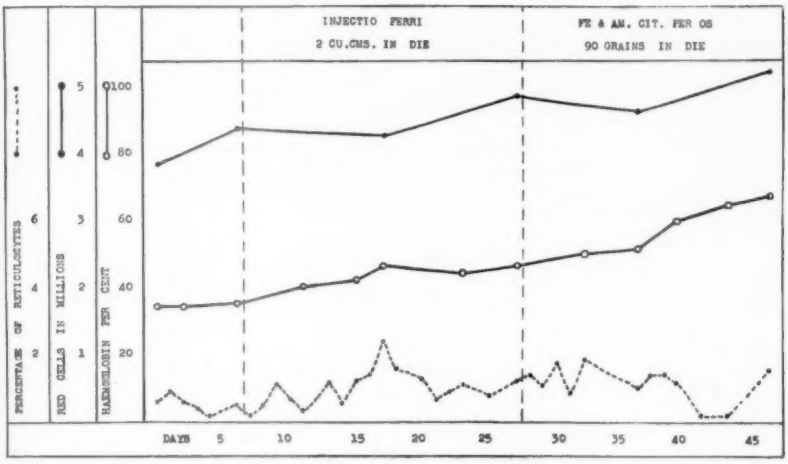

INJECTIO FERRI
2 CU.CMS. IN DIE
FE & AM. CIT. PER OS
90 GRAINS IN DIE
PERCENTAGE OF RETICULOCYTES
RED CELLS IN MILLIONS
HAEMOGLOBIN PER CENT
DAYS 5 10 15 20 25 30

CASE 3. FANNY R., 41. IDIOPATHIC HYPOCHROMIC ANAEMIA.

FIG. 3.

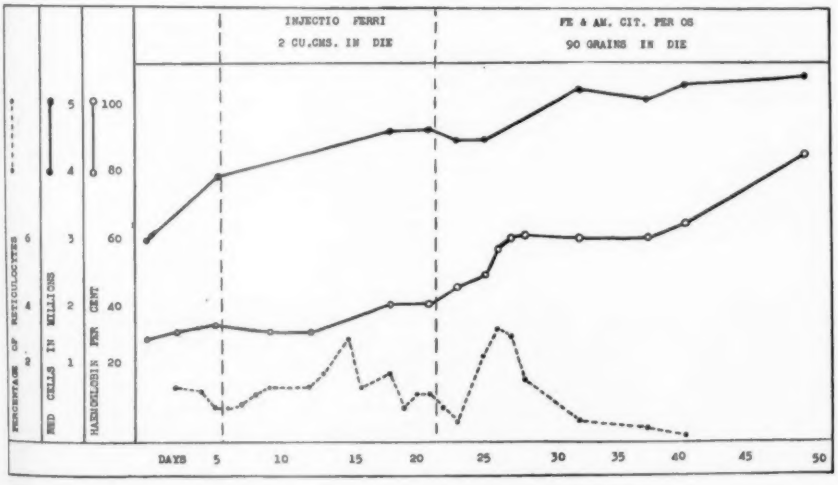
her teeth had been removed some months previously. Her blood-count was: red cells 4,600,000; white cells 4,000; Hb. 48%; C.I. 0·5. On treatment with Injectio Ferri B.P., 2 c.c. daily for ten days, she had a small reticulocyte crisis with a peak of 1·8%, and the hæmoglobin rose from 48 to 60%. Iron and ammonium citrate was then administered by mouth, when there was a more sustained reticulocyte crisis with a peak of 2·4% and the hæmoglobin rose from 60 to 74% in seventeen days.

IV. *Rheumatoid arthritis with achlorhydria and anæmia.*—Emily W., aged 52, had had rheumatoid arthritis since the age of 16. She had been an in-patient on this account at the age of 47, when anæmia and glossitis were noted, but not treated. The anæmia had been aggravated by influenza a few months before her re-admission. She was a typical case of



CASE 4. EMILY W., 52, RHEUMATOID ARTHRITIS

FIG. 4.



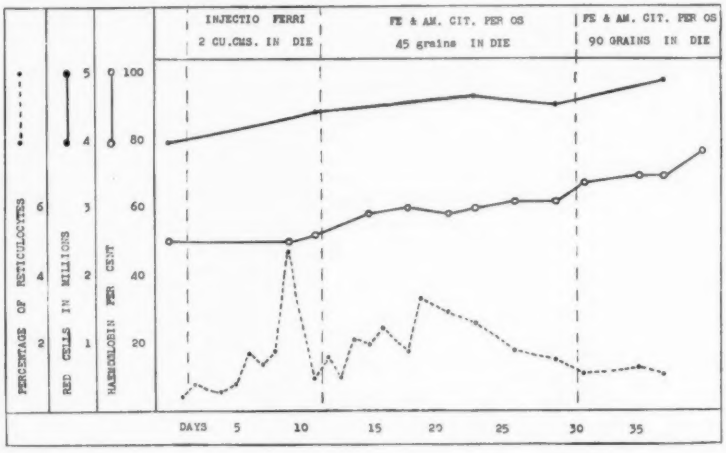
CASE 5. MARY ANNS W., 55, PLUMMER-VINSON SYNDROME.

FIG. 5.

rheumatoid arthritis, but was afebrile and had a normal pulse-rate. There was complete achlorhydria. The blood-count was: red cells 3,840,000; white cells 6,000; Hb. 34%; C.I. 0·45. She was given daily injections of 2 c.c. of Injectio Ferri B.P. for twenty-one days;

there was a long drawn-out reticulocyte crisis with a peak of only 2·4% and an increase of hæmoglobin from 35 to 46%. Treatment was then changed to iron and ammonium citrate, 90 gr. a day by mouth, when there was a further slight reticulocytosis and the hæmoglobin rose from 46 to 68% in nineteen days.

V. *Plummer-Vinson syndrome with achlorhydria.*—Mary Anne W., aged 55, complained of dyspnœa, glossitis and dysphagia. She had been an in-patient in the hospital on account of similar symptoms at the age of 41. The liver and spleen were palpable, a test meal showed complete achlorhydria, and on œsophagoscopy a stricture was found at the crico-pharyngeal junction and was dilated. The blood-count was: red cells, 2,980,000; white cells 4,900; Hb. 30%; C.I. 0·5. Injectio Ferri B.P. was injected in a daily dose of 2 c.c. for sixteen days; there was a reticulocyte crisis with a peak of 3%, and the hæmoglobin rose from 34 to 40%. She was then treated with iron and ammonium citrate by mouth, 90 gr. a day; there was a second reticulocyte crisis with a peak of 3·3%, and the hæmoglobin rose from 40 to 85% in twenty-nine days.


INJECTIO FERRI
2 CU.CMS. IN DIE
FE & AM. CIT. PER OS
45 grains IN DIE
FE & AM. CIT. PER OS
90 GRAINS IN DIE
PERCENTAGE OF RETICULOCYTES
RED CELLS IN MILLIONS
HAEMOGLOBIN PER CENT
DAYS 5 10 15 20 25 30 35

CASE 6. EDWARD J., 41. GASTRIC ULCER

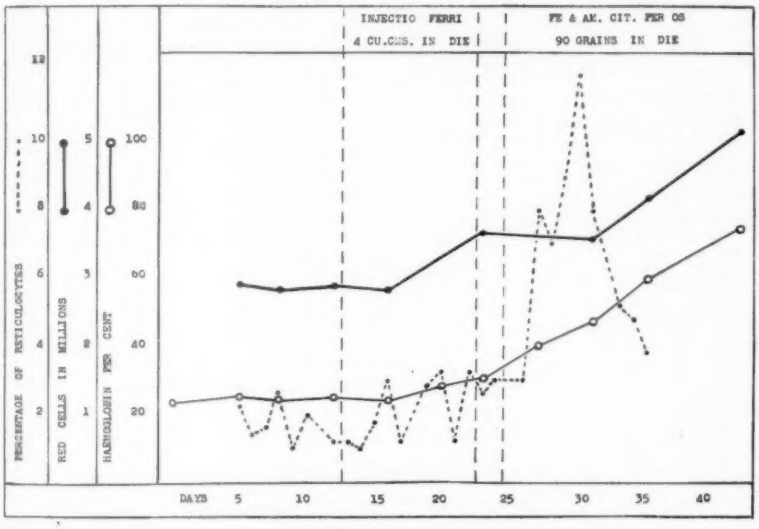
FIG. 6.

VI. *Gastric ulcer with anæmia and extreme hypochlorhydria.*—Edward J. first came under treatment for dyspepsia and anæmia at the age of 41. He had had empyema of the left lung in infancy and a gunshot wound of the same lung in the war, which had left him with bronchitis and asthma. He had also had slight bleeding from hæmorrhoids, which were treated by injection. The only other abnormal sign was hypochlorhydria. Under treatment with Blaud's pill, gr. 15 a day, his hæmoglobin rose from 50 to 70% in seventeen days.

He returned to hospital with similar symptoms at the age of 43. X-ray examination now showed a shallow ulcer high up on the lesser curvature of the stomach, there was complete achlorhydria in a fractional test meal, and the stools contained a trace of occult blood which rapidly disappeared on dieting. His blood-count was now, red cells 4,000,000; white cells 6,900; Hb. 50%; C.I. 0·6. On ten days' treatment by daily injections of 2 c.c. of Injectio Ferri B.P., he had a reticulocyte crisis with a peak of 4·3%, but the hæmoglobin only rose from 50 to 52%. He was then treated with iron and ammonium citrate, 45 gr. a day by mouth, when there was a second reticulocyte crisis with a peak of 3·3%, and an increase of hæmoglobin from 52 to 68% in twenty days. The dose of iron and ammonium citrate was then increased to 90 gr. a day and his hæmoglobin rose from 68 to 78% in nine days.

VII. *Anæmia and vertigo associated with dental sepsis.*—Benjamin B., aged 63, complained of brief attacks of nausea and vertigo of three months' duration. His teeth were extremely bad and he was very pale, but careful examination revealed no other signs of organic disease. The gastric secretion was normal. When first seen his hæmoglobin was only 55%, but a month later the blood had improved spontaneously, the count being: red cells 4,100,000; white cells 5,000; Hb. 72%; C.I. 0·9. He was then given ten injections of 2 c c. of Injectio Ferri B.P. in a period of twelve days, and at the end of this time the blood was practically unchanged (red cells 4,470,000; Hb. 75%). Treatment was then changed to iron and ammonium citrate, 90 gr. a day by mouth, and the teeth were extracted. Three weeks later the blood-count was: red cells 4,870,000; Hb. 80%. At no time was there a reticulocyte crisis.

VIII. *Anæmia from carcinoma of the stomach.*—William W., aged 72, had been losing weight for two and a half years and had been anæmic for one year. A test meal showed achlorhydria with persistent bleeding and the stools always contained occult blood in considerable amounts. The X-ray appearances were suggestive of a neoplasm on the lesser



CASE 9. CATHERINE G., 38, IDIOPATHIC HYPOCHROMIC ANAEMIA.

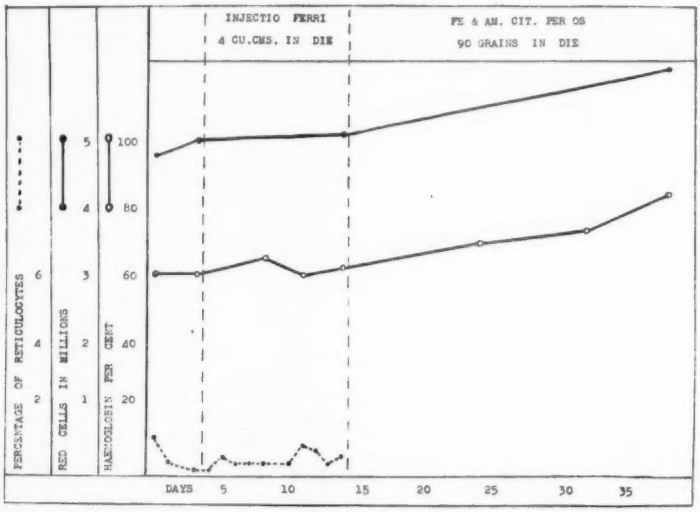
FIG. 7.

curvature of the stomach. The blood-count was: red cells 3,340,000; white cells 10,000; Hb. 45%; C.I. 0·7; the reticulocytes fluctuated between 1·0 and 1·7%. On treatment with eight daily injections of 2 c.c. of Injectio Ferri B.P., the hæmoglobin sank from 40 to 36% and the maximum reticulocyte count was 2·2%. He was then given ferrous sulphate by mouth in a dosage of 60 gr. a day; the hæmoglobin remained fixed at 36%, and there was an irregular reticulocytosis with a maximum of 5%.

IX. *Idiopathic hypochromic anæmia with achlorhydria.*—Catherine G., aged 38, had always been pale but had had more definite symptoms of anæmia for the past year. Physical examination was negative but a fractional test meal showed only a trace of free hydrochloric acid in the gastric contents. The blood-count was: red cells 2,920,000; white cells 6,600; Hb. 25%; C.I. 0·4. On treatment by injection of 4 c.c. of Injectio Ferri B.P., daily for ten days, there was an irregular reticulocytosis with a maximum of 3·2% and the hæmoglobin rose from 25 to 30%. She was then given 90 gr. of iron and ammonium citrate a day by mouth, when there was an unusually large reticulocyte crisis with a peak of 12%, and the hæmoglobin rose from 30 to 75% in nineteen days.

X. *Idiopathic hypochromic anæmia with normal gastric secretion.*—Dorothy T., aged 28, had previously been treated in the hospital for anæmia of the chlorotic type at the age of 24. On re-admission to the hospital she had well-marked koilonychia, the test meal showed hyperchlorhydria. The blood-count was: red cells 4,800,000; white cells 9,100; Hb. 60%; C.I. 0·6. On treatment with eleven daily injections of 4 c.c. of Injectio Ferri B.P., there was no reticulocytosis and the hæmoglobin rose only from 60 to 62%. She was then given 90 gr. of iron and ammonia citrate a day by mouth, when the hæmoglobin rose from 62 to 85% in twenty-four days.

We can dismiss the case of toxic anæmia and the carcinoma of the stomach from further attention, as neither patient reacted definitely to iron parenterally or by mouth. Of the remaining eight cases, all of which subsequently responded well to iron by mouth, two did not respond to the injection of iron, in Case II 2 c.c., or 7 mgm. of metallic iron daily for ten days, and in Case X 4 c.c. or 14 mgm. of



CASE 10. DOROTHY T., 24. IDIOPATHIC HYPOCHROMIC ANÆMIA.

FIG. 8.

metallic iron daily for eleven days. Iron was always more effective by mouth than by injection, as shown by the occurrence of a second reticulocyte crisis in every case. Case III was the only one in which the increase of hæmoglobin during the injection of iron—a rise of 1·2% a day—was greater than during the administration of iron by mouth, a rise of 0·82% a day. The average rise of hæmoglobin during the administration of iron by mouth was 1·32% a day, more than three times the average rise of hæmoglobin during the injection of iron, which was 0·4%.

It is clear from these results that hypochromic anæmia in human patients can sometimes be repaired by the injection of iron, but this method of treatment is much inferior to the administration of large doses of iron by mouth. It is fairly certain from the work of Heath and co-workers, and Fontés and Thivolle, that iron absorbed by the body in anæmia, whether parenterally or by the alimentary tract, is converted roughly quantitatively into hæmoglobin. Iron is not a mysterious stimulus to the bone-marrow but a raw material for the manufacture of hæmoglobin.

Calculation from our average values for the increase in hæmoglobin during the injection of iron shows that to cure an anæmia of ordinary severity it would be necessary to inject the maximum official dose of Injectio Ferri B.P. every day for four months. The only safe way in which to obtain approximately as good an effect with iron by injection as by mouth, would be to inject double the maximum official dose of Injectio Ferri B.P., i.e. 4 c.c. or 14 mgm. of metallic iron, twice daily for about six weeks. In the great majority of instances such therapy would be intolerable to the patient, and fantastically expensive as compared with the administration of iron by mouth.

The quantitative objection to parenteral iron therapy may be illustrated in another way. The average woman has a total volume of about 5,000 c.c. of blood. To increase her hæmoglobin from 35 to 100%, the task with which she is faced in a severe hypochromic anæmia, she must manufacture 10 grm. of hæmoglobin per 100 c.c. of blood, or 500 grm. of hæmoglobin in all. As hæmoglobin contains 0·3% of metallic iron, she will need 1,500 mgm. of metallic iron for this purpose. If she received 4 c.c. of Injectio Ferri twice daily, i.e. 28 mgm. of metallic iron a day, and if she converted the whole of the injected iron into hæmoglobin, she would still be unable to raise her hæmoglobin to normal until she had had fifty-four days of this treatment. It is interesting to see how closely the result of this theoretical calculation agrees with the estimate made in the preceding paragraph from the rate of increase in hæmoglobin actually observed in these experiments.

In conclusion, we can only reiterate our opinions in the words of Heath, Strauss and Castle, that weekly or bi-weekly injections of iron, especially when minute doses are given, are practically useless, and that, except in rare instances, the administration of iron by the parenteral route should be avoided.

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The Toxic Effects of Substances of the Carbon Tetrachloride Type

By Sir WILLIAM WILLCOX, K.C.I.E., C.B., C.M.G., M.D., F.R.C.P.

SUBSTANCES of the carbon tetrachloride group are coming into increasing use for many commercial purposes, and we are meeting with cases showing their toxic effects. The group is a fair-sized one, and the toxic effects vary according to the time factor, and many other conditions, as I shall be able to illustrate.

These substances have been known for many years, and on looking into the old literature we find that many of them have been used for anæsthetic purposes and afterwards discarded. Carbon tetrachloride, for example, was used many years ago, i.e. at about the time that chloroform was introduced. It was found to be inferior as an anæsthetic and more dangerous than chloroform and its use for that purpose was discontinued. So, though toxic effects from these substances are now coming to light, we find that they also occurred and were known years ago.

All these drugs are anæsthetics; they have a toxic effect on the brain, they are fat-soluble and are quickly absorbed, and they act on the grey matter, producing narcotic effects.

On several occasions I have called attention to the danger of liver poisoning arising from this group of drugs which cause toxic jaundice. The liver is the great

protector against poisons; it is the organ which usually is the first to give up its life, as it were, for the sake of the rest of the body, by absorbing the poison, so that effects on the liver are common and are well known. It has always been my belief that the toxic effects of a drug depend on the percentage of it in the blood at any particular instant. That is especially so with a drug like chloroform. Waller showed that if you have 6% of chloroform in the air which is inhaled, a few breaths of it may kill, whereas you may breathe a 2% chloroform vapour for many hours without experiencing danger. That is the explanation, I think, of the variability of the toxic effects. For example, in 1909 a young woman was having her hair shampooed with carbon tetrachloride at a London store, when she fell back dead. The experiments which one made at that time showed that in shampooing hair you might get about 5% tetrachloride in the air, the inhalation of which would cause a relatively high concentration in the blood. This girl died of heart failure; the poison acted on the heart muscle, and probably that was the cause of the death.

With regard to its use as a shampoo for ladies, so much publicity arose from this case that Sir Archibald Bodkin, who defended for the stores, and appreciated the danger involved in this use of carbon tetrachloride, agreed to the abolition by the Home Office of its use for this purpose. I have recently found that carbon tetrachloride mixed with petrol is being used by hairdressers, and have seen a case of faintness followed by jaundice and liver disturbance from the use of the mixture.

One knows that in the terminal effects of "hypohepatism," i.e. the cessation of liver function consequent on acute necrosis of the liver (acute yellow atrophy) jaundice occurs as do all the other effects of damage of the liver with loss of function. In these cases in the last two or three days there occurs a rise of blood-urea, the presence of albumin and casts in the urine, also red blood-cells in the urine. In other words, the kidney meets its fate soon after the liver function is checked, and the disability of the two organs goes hand-in-hand.

Recently I saw at the Royal Naval Hospital at Chatham, three cases under the care of Captain S. F. Dudley, R.N., F.R.C.P. The patients had been submitted to the vapour of carbon tetrachloride from fire extinguishers. In all of them, probably due to the rapid way in which the vapour was inhaled, the impact of the poison fell, not as I thought it would do, on the liver, and not on the brain, but on the kidney and all three patients had marked impairment of renal function. One case was one of the most remarkable that I have seen; there was a complete suppression of urine for ten days. Thanks to the efforts of Captain Dudley and his colleagues, the patient recovered and is now well. Ten days is the longest period of suppression of urine after which I have known recovery to ensue. The remarkable phenomena of this man's illness were due to the cessation of renal function for ten days. There was one other case, which I did not see, but of which careful records have been kept.

Below I will give the names of some of the substances in this group, and their properties.

Methyl chloride (CH_3Cl) is a gas, which boils at $-23{\cdot}7°$ C. It is used for refrigerators, and these refrigerators sometimes leak. In America a number of cases have been reported of methyl-chloride poisoning due to leakage from refrigerators. It has a toxic action on the nervous system, and the symptoms produced are of cerebral type.

Dichlormethane (CH_2Cl_2). This boils at 42° C. and it was used some years ago as an anæsthetic. Fatalities from this use were reported in 1869, 1884, 1890, 1891. In consequence of its danger as an anæsthetic its employment was given up. It is a fat solvent.

Chloroform ($CHCl_3$). Boiling point 61° C. This has been used for a great many years as an anæsthetic, and occasionally toxic effects occur, owing perhaps to a special

hypersensibility to the drug. You are familiar with the toxic effects of chloroform in causing respiratory or cardiac failure. Less commonly delayed chloroform poisoning may occur in which there is a "knock-out" toxic blow on the liver, causing defect of liver function, jaundice and death; while in the terminal stages of this condition the kidney is affected and uræmia also occurs.

Carbon tetrachloride (CCl_4). This boils at 76° C. It has been used as an anæsthetic, but its use was given up. It is now largely employed as a solvent for dissolving fat, resins, etc. It is also used internally for ankylostomiasis. A considerable number of deaths have been recorded as resulting from this, and there has been found acute necrosis of the liver (acute yellow atrophy) and in other cases cirrhosis of the liver with marked evidence of damage to it.

Most of these substances are non-inflammable. Carbon tetrachloride is used in a special type of fire extinguisher; the substance is squirted on to the fire and the vapour, which is over five times the density of air, puts out the fire by preventing the access of air. This vapour is very toxic. I would again call your attention to the risk of suppression of urine and the danger of renal damage from the use of fire extinguishers containing carbon tetrachloride.

In the case which I mentioned above a fire had occurred in the chart-room of a ship, and twelve times the patient went into that room, for two minutes each time, and squirted this substance on to the fire. In doing so, he naturally inhaled a large quantity of the vapour. Two days afterwards his kidneys refused to act. The fire occurred on May 3, 1933, and from May 5 to May 16, he passed only 23½ ounces of urine, and even this had to be drawn off by the catheter. The urea was 112 mgm. per 100 c.c. on May 7, 281 mgm. per 100 c.c. on May 15. There was no jaundice, nothing more than a slightly yellow look, the icterus index being only the maximum of what is regarded as normal. At the end of ten days the kidneys began to work again, and the patient made a good recovery. During the uræmic period muscular twitchings occurred but no convulsions. He had persistent vomiting with hæmatemesis and melæna. When the kidneys began to recover from the toxæmic condition as shown by the passage of urine, recovery from the symptoms and uræmic state was rapid.

It is important that notice should be taken of this most remarkable case because these fire-extinguishers are being largely used. In the three other cases the uræmia was so latent that if the blood-urea had not been tested and the urine examined it would scarcely have been recognized that the symptoms were due to the effect of carbon tetrachloride on the kidney. In one of the cases several severe convulsions occurred. I do not propose to give further details of these cases because they are being published by Captain Dudley.

Bromoform ($CHBr_3$). Boiling point 148° C. I include this among the substances because it is occasionally used for whooping-cough. That is practically the only purpose for which it is employed. It is a dangerous toxic substance and there have been deaths recorded from its use.

Ethylene Group.

Di-chlor-ethylene ($C_2H_2Cl_2$). This boils at 48° C. or 60° C. There are two isomeric forms. It is used for the removal of fats, and sometimes for dissolving iodine, for surgical purposes. It is a toxic substance.

Tri-chlor-ethylene (C_2HCl_3). Boiling point 88° C. This has been largely used commercially for removing fat and as a solvent. It has also been employed as an anæsthetic, but it does not keep very well, and it is not such a safe anæsthetic as chloroform. I saw in November 1932, a case, which was under my colleague Dr. Reginald Miller, to whom I am indebted for publishing this account. The patient (R.P.) was a boy aged 16 and he was engaged in some works where safety-razor blades are plated. Before admission to hospital he had had jaundice for a month, and he

was admitted to St. Mary's Hospital under Dr. Miller on October 19, 1932. The icterus index was 240; there was a little albumin in the urine, he had frequent vomiting but the temperature was normal. The liver was enlarged, but the gall-bladder was not. The van-den-Bergh test showed an indirect positive, and, as is found in these deeply jaundiced cases, a bi-phasic reaction. It was obviously a toxic and not a catarrhal jaundice. He had jaundice for three months. The lævulose test for liver function was positive, showing defective function of the liver. Gradually the jaundice cleared up, the liver became normal in size and the boy recovered.

Dr. Reginald Miller asked me to see this patient, and I at once suspected one of these toxic substances as the cause. The boy told me that his work consisted in dipping safety-razor blades into a sweet-smelling liquid, which was contained in a tub. This removed the fat, and then the blade was plated. On inquiry we found that there had been other cases of illness in the factory, amongst those engaged in the same occupation, though no others with such deep jaundice. It became evident that this was a case of toxic jaundice due to inhalation of tri-chlor-ethylene vapour.

Tetra-chlor-ethylene (C_2Cl_4). Boiling point 110° to 120°. Sometimes used as a solvent of fats, is very toxic.

Ethane Derivatives.

Ethyl chloride (C_2H_5Cl). Boiling point 12° C., is a volatile liquid. It is used as a local—and also as a general—anæsthetic. It is not very toxic, but there have been cases of death from its action on the brain and the heart, also from its effect on the liver, causing toxic jaundice.

Tetra-chlor-ethane ($C_2H_2Cl_4$). Boiling point 140° C. This is rarely used now, but it was largely in use before the war. It is a solvent of cellulose. Just before and in the early days of the war it was used as a constituent of the cellulose solution for varnishing aeroplane wings, and, as you remember, there was a great outbreak of toxic jaundice in all the aeroplane factories of the country. The first case (G. M.) of the kind came to my out-patient department at St. Mary's Hospital in 1914. I diagnosed it as toxic jaundice due to some chloroform-like substance. The patient was admitted as an in-patient to another hospital where his case was diagnosed as one of acute yellow atrophy of the liver. The man died, and owing to the representations of his widow that the death was due to his occupation, a coroner's inquest was held. Sir Bernard Spilsbury made the post-mortem examination and said that the death was probably due to some poison, the nature of which required investigation. The case came back again to me at this stage and we carried out investigations. We were informed of the composition of the cellulose varnish and it was clear that the toxic constituent was tetra-chlor-ethane. We found that it caused acute yellow atrophy in animals if it had been inhaled by them, and that this was undoubtedly the substance which had caused this patient's death. I afterwards inspected many of the aeroplane factories in which this cellulose varnish was used and found large numbers of cases of incipient jaundice amongst the workers; several suffered from vomiting in the morning, headache, drowsiness and slight icterus. I also found some cases of cirrhosis, with ascites in people who had been exposed to this substance. A number of deaths occurred from toxic jaundice amongst these workers. As a result of these investigations the use of tetra-chlor-ethane was abolished. Some other solvent of cellulose was discovered, which was non-toxic, and now practically no cases of the kind occur. However, this substance is still used occasionally as a solvent of cellulose for varnishing small articles, and the late Sir Thomas Legge told me that several cases had been reported of jaundice from tetra-chlor-ethane when it was used on a small scale, showing how dangerous it is.

Section of Odontology

President—Sir NORMAN BENNETT, M.B., B.Ch., L.D.S.E.

[*October* 23, 1933]

State-aided Dental Research

PRESIDENT'S ADDRESS

By Sir NORMAN BENNETT, M.B., B.Ch., L.D.S.E.

BEFORE the days of the Medical Research Council and the Dental Board I often used to think, when puzzling over some of the problems of dental pathology, how much might be done if there were only a little money to play with, and how, if there were enough to remunerate adequately whole-time workers with brilliant minds, the prevention of dental diseases might become a real possibility instead of a chimæra.

We have now had twelve years of subsidized dental research, and most of the results have been published, and I shall perhaps be interpreting men's minds fairly correctly if I say that the general impression is that while a large amount of excellent detailed work has been done, we are not very much nearer the goal of effective prevention of dental caries and parodontal disease than we were twelve years ago. I believe that that impression does less than justice to the workers and those who have assisted them. The difficulty is to see the results whole, or even as a group of aggregations of small units. It is like taking up a jig-saw puzzle containing a few islands of already fitted pieces. There are some useful bits, obviously of the right colour, which may help to unite the other portions if we can fit them in. It seemed to me that I might best show my appreciation of the honour you have bestowed on me in making me President of this Section, by briefly recounting the history of subsidized dental research in this country, and more particularly by trying to synthesize the results, by venturing to estimate their relative importance, by showing how well some of them fit together, and how others perhaps seem as if they can never form part of the picture. I cannot hope for any striking success in these efforts, but if the result should be to indicate ever so vaguely the paths that we need to tread, and to illuminate them ever so dimly, then something useful will have been done. Prior to 1921 the Medical Research Council had assisted research in matters connected with the teeth, but there was no special Committee of the Council which might be expected to suggest means for a concerted attack on the major problems of dental disease. There was singularly little difficulty about its inception. The matter was first discussed with Sir George Newman, who promised all facilities from his department, and Sir Walter Fletcher, when approached, at once took the problem up with the enthusiasm that always characterized him when

he saw opportunities of steady progress on sound lines. Let me say here that I think only the members of the Dental Committee realize what a good friend dental research has lost in Sir Walter Fletcher. He gave the Committee his confidence, he was always encouraging and sympathetic, and was wisely critical on rare occasions.

The Committee first met on October 21, 1921—only about two months after the passing of the Dentists Act—under the chairmanship of Professor Halliburton. I am not proposing to say much about the personnel of the Committee, but I should like to pay a tribute to the work of the late Dr. Langdon who was its secretary for most of the period of twelve years during which it has been in existence. He took a deep interest in all the problems that arose, applied his alert and active mind to their solution, was sympathetic and tactful with the research workers, and as a secretary was efficiency itself.

The first work of the Committee was to collect existing information and facts on the problems of dental disease. This was not very illuminating or productive, and the Committee felt that at least it would be useful to have a really accurate knowledge of the character and extent of dental disease in children. They therefore enlisted the services of Mr. Norman Ainsworth [1], who examined 4,258 children in thirty-six schools chosen to provide the widest variety in regard to geographical, physical, and industrial conditions. I think that his investigation was, and remains, the most scientifically conducted of its kind that has been undertaken in this country, and it provided valuable information concerning dates of eruption, the incidence of caries, the surface distribution of caries in permanent teeth, and arrested caries in deciduous teeth. Among other results Ainsworth definitely established the fact that teeth affected by gross hypoplasia were more susceptible to caries than others, and that the hypoplasic areas were the most susceptible. He also found that 23·2% of children examined exhibited in varying degrees unilateral or bilateral antero-posterior malocclusion. These facts will be of interest presently in conjunction with the results of other research work.

I shall now disregard historical sequence and try to view the various problems from an entirely different standpoint, namely, the tissues, organs, diseases, or malformations, upon which light has been thrown by the concentrated beams of different research workers.

In the hope of solving the problems of dental caries and parodontal disease it is natural that so far as anatomy and physiology are concerned workers should have concentrated on the enamel, and on the point of junction of the cementum, periodontal membrane. and gum epithelium. Let us first consider the former, which has been investigated in several ways.

Mummery [23], in a Medical Research Council Report in 1923, gives an excellent résumé of the evidence for and against an organic content in enamel. As everyone knows, Tomes concluded that there was practically no organic content, but that what had been thought to be a small organic constituent was only water of crystallization. Lovatt Evans found 1 to 2% of organic material. Leon Williams, Walkhoff, and Hopewell Smith regarded the enamel as a dead structure. Fisher and Von Beust regarded the enamel as being in vital organic association with the dentine. Douglas Caush had long ago demonstrated that stains would penetrate enamel between the prisms. Ebner, Gottlieb, Pickerill, and Mummery, by various methods of staining, confirmed this, and Pickerill found that staining from the external surface became more difficult in older teeth.

Malleson [12], working in conjunction with Laidlaw, devised a very special, elaborate and difficult technique for cutting sections of decalcified enamel. He was able to show (in 1924) that after decalcification a very delicate network on the surface of each enamel-prism remained—a prism-cortex. He also found that the surface layer of the enamel sometimes appeared to be of a homogeneous nature

without distinction of prisms. The form of the prisms was not hexagonal as had usually been thought, but round or ovoid in section, and often grooved on one side like the prisms of elephant's enamel described by Mummery. I suggest that this grooving may serve to give strength or rigidity, as in the longitudinal ridge on the wings of motor cars.

Sprawson and Bury [27], in 1928, by very careful estimation of nitrogen and the organic carbon, concluded that Tomes was correct; but in 1930 Sprawson [28] published a very interesting investigation of marsupial enamel, and (to a less extent) of human enamel, in which he showed that cracks in marsupial enamel were associated with increased patency of the adjacent dentinal tubules and of the inter-prismatic substance of the enamel, and that closure of the cracks took place from without inwards by hypercalcification. This is, perhaps, easily credible in the case of marsupial enamel, but Sprawson shows similar appearances in human enamel, which are at least suggestive. These observations must be taken in conjunction with those of Mummery, who showed that an appearance resembling the translucent zones in dentine sometimes occurred in enamel in response to surface lesions.

Fish [7] confirmed the work of Malleson on the organic cortex of the enamel-prisms. He also showed that the enamel of dogs was permeable by simple diffusion from both surfaces, but that with age a change occurred in the outer part of the enamel which rendered it impermeable. Human enamel was impermeable by simple diffusion under the conditions of his experiments.

Jeffery, working in conjunction with Laidlaw, made a large number of experiments on canine and human enamel in forcing dyes through enamel by means of cataphoresis. He found that dog's teeth were readily permeable. In a recently erupted canine of a dog five months old, acid-fuchsin was made to pass right through in ten minutes. Permeability decreased with advancing age, but the surface enamel for the thickness of about 5μ was almost impenetrable from within. The staining passes through the prism-sheath or cortex. In human teeth the staining was more difficult; it required a current of higher voltage (up to 200); the staining was more patchy, and showed no correlation with age or other conditions; and secondary dentine or the translucent zone formed an effective bar.

Jeffery experimented with various salts and found that the permeability for different substances varied considerably. In a later series of experiments he devoted his attention to permeability to different forms of phosphate, as this seemed to have a possible connexion with late calcification. He found that young dogs' teeth were more permeable to organic phosphates—hexomonophosphate and especially glycero-phosphate—than to inorganic phosphates. He further found that the enzyme phosphatase was present in the pulps of dogs' teeth, especially of young dogs, and to a slight extent in the hard tissues, but in human teeth, permanent and deciduous, the enzyme could only be identified in the pulps. These observations should be taken in conjunction with Robison's theory that hydrolysis of organic phosphates by phosphatase raises the concentration of inorganic phosphate in tissue-fluid and so enables calcium phosphate to be deposited.

I have given you a brief résumé of most recent British work on the structure and functions of the enamel. What can we glean from it? It seems to me that there is definite proof from permeability experiments that the enamel is not a solid block of calcified material, and also that whatever the chemical analyses may say, the histological evidence is sufficient to show that there is a definite organic content and structure. To what extent, if at all, is the enamel vital? The observations of Mummery and Sprawson indicate the possibility of vital reaction. The relatively harder outer skin of enamel is, I think, definitely established. One may assume that it is mechanically protective and probably also protective against harmful permeability from without. I suggest that there is here a close analogy with the

superficial layers of the epidermis, which certainly are mechanically protective, which form an effective bar, when uninjured, to microbial invasion, but which do allow the absorption of medicaments from without under certain conditions. Jeffery's experiments show, at any rate in dogs' enamel, that the enamel becomes less permeable with age, and as regards human teeth this accords with the vast body of clinical experience. But chemical analysis has never shown that old teeth have a higher calcium-content than young teeth ; such evidence as there is points the other way. I have always felt that some difference in physical structure might account for increased hardness. Investigations of the crystalline structure of enamel by means of X-rays are now being carried out at the National Physical Laboratory by Dr. Shearer and Mr. Thewlis [24]. The results so far are incomplete, but they do give further proof of the existence of the hard outer layer, and they afford some indication that this hardness may be associated with parallelism of the crystals, compared with the random orientation of other parts, just as rolled gold is harder than annealed gold. More than that I must not say (perhaps I should not have said as much), but the results of further work will be awaited with much interest. I conclude, then, that the enamel is a vital structure nourished from within as far as its extreme outer border, and possibly accessible in a small degree to influences from without. I am confirmed in this view by the belief that no part of the human body is completely cut off from vital influences. One thinks at once of the skin, the hair, and the nails. The hair certainly is not dead. Both in animals and human beings it varies in condition to a remarkable extent in conformity with changes in conditions of general health. This variation can hardly be accounted for by the effect of external secretion around the base of the hairs, but must rather be due to changes in the internal channels of the hairs themselves. The nails are keratinized, but we do not know that they are completely removed from vital influences. Fish [7] regards the hardening of enamel after eruption as a process of keratinization of the enamel-sheaths, and observes that Nasmyth's membrane and enamel lamellæ are definitely horny structures, and are in close association with the enamel-sheaths. He is drawn to this conclusion partly by belief that calcification, in the true sense of the word, cannot take place apart from a cell-mechanism. That may be so, but I do not think it is necessary to envisage the hardening process which takes place, chiefly towards the outer surface, as either calcification in the ordinary meaning of the word, or else keratinization as the only alternative. There may be molecular or crystalline changes with or without increased calcium-content, assisted from within or even from without, which account for increased hardness. However that may be, all the work to which I have referred tends to show, and in a marked degree some of it does show, that the enamel is an organic and vital structure, and unless more proof is forthcoming to the contrary, I shall for my part place no limit to the boundaries of the enamel to which that vitality extends.

We may now proceed to a consideration of the problem of dental caries. I shall assume that the chemico-parasitic theory—the decalcification of enamel, the invasion by micro-organisms, the proteolytic destruction of the organic content of the dentine, adequately explain the actual process, but tell us nothing about the varying degrees of immunity and susceptibility in different races, different people, and different members of the same family. There are I think three factors, and only three, which enter into this variability—structure, nutritional influence from within, and external influences from the oral fluids or conveyed by them.

The first of these brings me at once to a consideration of the work of Mrs. Mellanby [14] [16] [17] [18] [19]. There may be some who do not quite appreciate the character and extent of the work that Mrs. Mellanby has accomplished, and are therefore inclined to under-estimate its importance. I think there has been some tendency to confuse the experiments themselves and the facts discovered by them with inferences concerning the bearing of these facts upon the question of susceptibility. For my

part I find the work most impressive. It has extended over many years and involved an enormous number of experiments; it has been carried out with extreme care for avoidance of error, with proper controls; and it has been assisted or checked by a vast amount of histological and chemical laboratory work. To my mind Mrs. Mellanby has established the following facts. In experiments on dogs:—

(1) Assuming a reasonable diet from the nutritional standpoint, and including of course calcium and phosphorus, teeth of good structure can be insured by giving vitamin-D in natural food, or in cod-liver oil, or as a synthetic product, or even by irradiation of the skin.

(2) Without a sufficiency of vitamin-D, defective calcification is certain.

(3) Variations in degree of calcification at different periods can be produced by changes of diet from time to time.

(4) Cereals possess a definite anti-calcifying property, the worst being oatmeal.

(5) Defective structure can be produced by feeding the mother on a diet deficient in vitamin-D, though this may be compensated to some extent by drawing on the maternal store.

In human teeth minor degrees of hypoplasia are extremely common, and consideration of the ordinary gross forms of hypoplasia alone gives an incomplete picture of the structure of human teeth in general. These results are based on the macroscopic and microscopic examination of a large number of teeth of which the majority were deciduous.

So much for structure. In passing to a consideration of internal and external influences one is faced with the difficulty that one factor may be operable in either way or both.

Mrs. Mellanby has published a series of papers on experimental work on children in conjunction with Mr. Proud and Dr. Pattison. In the first experiments with Dr. Pattison [20] three different diets were given to 71 children divided into three groups. It was found that with the best diet dental caries appeared to be inhibited and carious cavities became harder, and also the calcium-content of the saliva was increased. In a similar experiment [21] on 78 children vitamin-D produced similar results in inhibiting the caries. In a third experiment [22] on 22 children to test the effect of a cereal-free diet, it was found that the best results accrued from such a diet rich in vitamin-D; but it should be observed that this diet was singularly free from sticky carbohydrates and uncooked sugar. Broderick [3], in criticizing these results, argues that the variation in the acid-base ratio of the three diets in the first experiment was really responsible, and he believes that the anti-calcifying effect of cereals is due not to a definite factor but to an upset of the acid-base ratio.

Mellanby and Pattison's results are of course on a comparatively small number of children, but they were sufficient to justify the Council in initiating the much more extensive Birmingham experiments. The object was to test the effect of vitamin-D in one form or another: (*a*) On teeth developing while the diet was in progress, and (*b*) on the effect on dental caries in teeth already formed. The former, of course, needs many years to determine the results. The latter is now completed, and an interim report [6] has been published. The experiment was in two parts. In three different institutions containing 236 children in all, the children were given the same basal diet, but in one institution cod-liver oil was added, in another treacle, and in the third olive oil. There was a definite and significant difference, both in the incidence and extent of caries, between the cod-liver oil group and the other two, especially in the permanent dentition, and no appreciable difference between the treacle and the olive oil. A similar experiment was carried out on another 161 children with olive oil plus radiostol, and with olive oil, with similar results. The work was done with extreme care and precision, and was in

the hands of a competent dental surgeon, who made regular inspections, and of a lady assistant.

The results cannot be ignored. I find it difficult to believe that the effects, even upon the existing carious cavities, were produced through the medium of the saliva; if they were not, they must have been produced from within. One is reminded of the process of naturally arrested caries so common in deciduous teeth, but occurring also in permanent teeth. This condition is well described by Mummery [23] in an early report of the M.R.C. He defines a pigmented zone, which is resistant, and the well-known translucent zone underneath, which forms an effective barrier. The condition is produced, of course, partly mechanically, when the breakdown of the enamel walls has extended to those portions where the direction of the prisms is more or less radial to the centre of the crown; but there can be little doubt that we have also to do with a vital reaction. The condition occurred frequently during the War in the permanent teeth of recruits and soldiers when they came under an environment totally different from that of their civilian life, environment being taken to include diet and all other external conditions.

Fish [7] has proved that there is free communication between the pulp and the fluid contents of the dentinal tubules, but as there is no free intercommunication at the periphery of the dentine it is a little difficult to understand how the circulation is kept up. Fish is inclined to think that the fluid in the tubule is secreted by the fibril and that the circulation is centripetal, but this seems contrary to what one would expect, unless the calcification in the translucent zone, and possibly in the enamel, is provided for by secretion from the fibril deriving its supplies from the odontoblast and the pulp. Fish also finds that there is a physiological increase in the calcium content of the dentine with advancing years, which seems to indicate that whatever the exact process of primary calcification of the dentine may be, the Tomes' fibres do control calcification subsequently. The brilliant work of Fish on the reaction of the pulp and dentine to injury or caries throws further light on the possible effect of diet in inhibiting caries. He has demonstrated that the reaction is of two kinds. In coronal surfaces in molars it occurs usually as a band of hypercalcification in the tubules underneath the lesion, and in other parts as an area of secondary dentine at the pulp-margin, together with hypercalcification of the tubules adjacent to the affected area of dentine, which he describes as the dead area. This dead area remains to me something of a puzzle. Although there is no definite proof that it is dead, it has every appearance of being so, but, clinically, extensive cavities in the crowns of molars are often less sensitive than cavities in other parts, and I find it difficult to believe that when I am dealing with hypersensitive dentine I am always outside the dead area. However this may be, it does not affect the validity of Fish's work in showing the different ways in which reaction takes place; and the efficiency of the barrier of the translucent zone is further shown by Jeffery's demonstration that it is impermeable to electrically driven ions.

I think that these researches of Fish emphasize the protective and recuperative powers of the pulp and dentine, and we may perhaps add the enamel, in view of the work of Mummery and Sprawson, and there is nothing unreasonable in supposing that the effect of vitamin-D in the diet is not limited to controlling the calcification of the developing tooth, but may also stimulate the defensive processes which are made manifest by the researches of Fish and the known facts of arrested caries.

Let us turn now to the saliva. This has been frequently investigated in different ways, because those searching for a solution of the problems of caries and parodontal disease have always felt that the fluid which bathes the teeth, and therefore acts as the carrier of protective or noxious influences, must be of importance. There is little that is really definite. Naturally the two points that have attracted most attention are the acid-base balance and the calcium-content. Spencer-Payne [26] considers

that no definite relationship between acidity or alkalinity and dental caries has been proved. He made investigations of the calcium content by Laidlaw's method, and was unable to confirm Bunting and Rickert's conclusions that it remained fairly constant for each individual, and that immune persons showed a higher content than susceptible ones. Kathleen Horton, Marrack, and Price [8] found that there was no great difference in calcium-content with different kinds of stimulation, but that there was variation at different times of day. There was a clear association of caries with a low calcium-content, a definite reduction of calcium with the progress of caries, and a higher calcium figure after dental treatment. This fact should be noted in connexion with Mellanby and Pattison's experiments [20] [21] [22], when they found that with the diet which had a beneficial effect on caries the calcium-content was increased; but whereas the latter experiments seem to suggest a dual result from the one cause, the former experiments seem to indicate definite effects on the calcium-content of the saliva following the progress and mechanical prevention of caries. Broderick [3], analysing the work of Starr and Bunzell, finds a significant difference in the acid-base ratio at different ages, showing relation to the varying susceptibility to caries and parodontal disease at different times of life. He attaches much importance to Weston Price's theory of the dissolution of the enamel when the saliva is on the acid side of what he calls the iso-electric point. With my very limited knowledge of bio-chemistry and bio-physics I find this theory very difficult to follow, and Broderick himself refers to it as a " visualization."

The Dental Committee felt that so far as the actual process of dental caries was concerned, no progress was likely to be made by investigating further the later stages of caries, but that a careful examination of the very earliest stages might lead to some significant results.

Dr. Kilian Clarke [5], following up the work of McIntosh, James, and Lazarus Barlow on *Bacillus acidophilus* discovered *Streptococcus mutans*. He concluded that whereas " *B. acidophilus* could be isolated only from teeth in which cavities had formed, or in which the foci of caries were shallow and contamination from the surface could not be excluded," " *S. mutans*, on the other hand, grew best in a medium with a reaction approximating that of the saliva, was found in the earliest stages of decay, and could be isolated in pure culture from carious dentine, and more or less efficiently protected from secondary infection or surface contamination." *B. acidophilus* " although it would grow in a neutral or slightly alkaline medium, preferred an acid one, and would therefore find suitable pabulum in carious cavities." He attached much importance to " the fact that colonies of *S. mutans* adhere closely to the surface of the teeth," because " a local concentration of acid in contact with the enamel is thereby produced, and this could obviously give rise to rapid decalcification, independently of the acidity of the medium as a whole." Maclean [11] in further experiments concluded that either organism was a possible factor in dental caries.

Malleson [13], investigating the early stages of caries in enamel, found that a very large proportion of teeth had cracks in the enamel. These were found in teeth extracted for orthodontic purposes, and on the surfaces of teeth not liable to injury. He found that the infection sometimes spread right down a crack, travelled for a short distance along the amelo-dentinal junction, and returned by another adjacent crack. These cracks have also been noted by Mummery [23]. Walkhoff stated that defects in enamel were very common, and Fish [7] describes the lamellæ in enamel. Malleson found also that early caries in enamel spread first through the inter-prismatic substance. He further confirmed the presence of the homogeneous layer of surface-enamel previously discussed.

I must not avoid the problem as to how far the facts and conclusions so far reached run counter to the popular belief that easily fermentable sugars and sticky carbohydrates are the main factors in producing dental caries. Mrs. Lindsay has

provided an analysis of 95 original papers bearing on this question, and Dr. Langdon furnished references to papers dealing with sweet-eating. Although no single instance may bring convincing proof, the cumulative evidence is enormous. We are all familiar with the frequent examples of native races living on a natural diet under primitive conditions who are more or less immune to caries, but become highly susceptible when coming under the environment of so-called civilized conditions. Then there are examples from British Malaya, Japanese children in Hawaii, and many other countries where special and peculiar diets seem to indicate particular conclusions, or where two different races living on different diets in the same country show different results as regards susceptibility to caries. There are Bunting and Regnart's significant effects of artificially produced caries under silk ligatures. This is comparable with the white line of decalcification under the small deposit of *materia alba* round the necks of teeth which we see so frequently in children whose mouths are not, generally speaking, unclean. I think it is true that during the War certain classes or groups of children who could not get the usual supplies of sweets were less susceptible to caries. I am satisfied that in my own practice the children of to-day are less susceptible to caries than those of twenty or thirty years ago. Whether this is due to improved methods of feeding of young children or infants, or to pre-natal nutrition I do not know—certainly the educated young mother of to-day is usually highly competent without being fussy. Nor do I know whether the lessened susceptibility is due to better structure, better feeding in a mechanical sense, diminution in fermentable carbohydrate, or a diet so well balanced as to keep the saliva on the alkaline side of pH7, and to ensure a sufficiency of calcium in the tissues and a sufficiently high calcium-content in the saliva.

I feel that the evidence for the direct effects of fermentable foodstuffs is very strong, and I ask myself how far it is in accord with the more definite experimental evidence or how far it clashes with it. At one time I thought that investigation of the dental condition of identical twins might throw a light on this problem. Miss Bachrach [2] examined 130 pairs of identical twins (of course of like sex) and 171 pairs of ordinary fraternal twins (of like or different sex), and the statistical results were prepared by Matthew Young. The results were disappointing. In regard to the total incidence of dental caries in the permanent dentition, identical twins were not more alike than fraternal twins. It is interesting to note, however, that the proportion of pairs in which gross hypoplasia was present in both twins was significantly higher in the identical twins than in the fraternal twins. This would seem to indicate that although hypoplasia is understood to be due to errors in infant feeding, and acute illness in later years, yet there is a congenital or hereditary factor not present in the figures of the incidence of caries.

The best-known and now classic example of immunity to caries is found in the island of Tristan da Cunha. The Dental Committee was interested in two visits to the island when examination of the teeth was undertaken. The second of these was the more complete and detailed, and was carried out by Surgeon Lieutenant-Commander (D) Sampson. It amply confirmed the remarkable freedom from dental caries but differed from the former report in another respect to be referred to presently. It is curious that such significant statistics about this island should be so inconclusive. There are no cereals; therefore the structure of the teeth is good. There is no sugar; and so there is no bacterial fermentation to start caries. There is an ample supply of potatoes; hence the large excess of base over acid in the diet, and the prevention of decalcification.

And now where are we? I am drawn to the conclusion that although the facts of the chemico-parasitic theory remain undisturbed as explaining the actual process, the tooth as a live organ, even including the enamel, and the body as a whole, are much more concerned with the process of caries than has hitherto been thought: dental caries is more truly a disease than was once thought, and the tooth not a mere

passive victim of external attack. I think there has been too much tendency in the past to look for one specific cause of dental caries and to believe that when that cause was found an easy remedy might be propounded.

Are the results so far achieved inconsistent? I venture to say not. Good structure is doubtless an important factor, but not necessarily, as Mrs. Mellanby herself says, the whole story. Too much carbohydrate of the wrong kind in the mouth may easily favour bacterial action upon enamel. A mouth kept clean by natural processes (possibly more effective than the occasional tooth-brush), if this can be achieved, will obviously tend to inhibit bacterial action. Are these results taken together inconsistent with Broderick's [3] theory? If I understand the theory correctly and may try to put it quite briefly, it is something like this: The acid-base balance of the saliva varies in conformity with that of the body. The calcium-content of the blood does not vary much, and can only with difficulty be raised above a certain point, and when the acid-base balance of the body passes to the acid side the reserves of calcium in the body are drawn upon for neutralization. When the saliva is acid the calcium of the enamel may be withdrawn. This reaction does not commence at any constant point of hydrogen-ion concentration, but depends upon what Weston Price describes as the iso-electric point, which is said to vary in association with different proteins in the saliva. The acid-base balance of the body is determined by a variety of conditions—the food, the vitamin-content, deficiency of oxygen, endocrine secretions, and emotional states. Broderick's views are, I think, largely theoretical, but are supported by a considerable weight of converging evidence. How far they will withstand criticism my very limited knowledge of biochemistry does not enable me to judge, but when I try to picture exactly what happens in the enamel I find it very difficult. If the effect of iso-electric acidity were to cause an obvious loss of calcium over the whole tooth surface that would be something definite. But an invisible molecular loss which is sufficient to favour the recognized initial process of solution by lactic or other acid at a particular point seems to me unsatisfying. Whether or not the enamel can, conversely, have its calcium restored to it remains undecided. The hardening of normal enamel after eruption is supported by clinical experience of young teeth, and teeth involved in parodontal disease, but it is more difficult to picture any kind of reconstruction of enamel partly destroyed by dental caries. I have sometimes thought that the white lines at the necks of teeth in children that I referred to just now did partly disappear, but have never been able to satisfy myself on that point. Whatever may be the truth about these things, it seems clear that at any rate there is nothing in Broderick's theory which is definitely inconsistent with the conclusions derived from the work of others.

Much less research has been done on behalf of the Council in the elucidation of the pathology of parodontal disease than of dental caries. Here again the precise histological state and relationship of the tissues have an important bearing on the morbid process. Mrs. Mellanby's experimental work [15] on dogs, rabbits, and rats is of extreme interest when taken in conjunction with the work of James and Counsell [9]. The first question is what is normal? Both workers and others do, I think, agree that the subgingival epithelium contains no papillary processes and does not extend down over the cementum, and that there is continuity from the squamous epithelium of the gum surface through the subgingival epithelium to Nasmyth's membrane. James and Counsell find that there is continuity between the superficial keratinized layer of the subgingival epithelium and Nasmyth's membrane, and that there is no appreciable sulcus between the gum-margin and the enamel, but that the two meet at an angle. Now the interesting point is that the changes in the soft tissues which James and Counsell describe as characteristic of the disease, namely, proliferation of the epithelium, irregular finger-like processes, spread of epithelium down the cementum, concentration of cells in the corium, conversion of bone into osteoid tissue, are paralleled by what Mrs. Mellanby has produced in animals by

feeding experiments. Mrs. Mellanby has shown that whereas the hard structures are dependent for their full development on vitamin-D, the soft tissues in the neighbourhood are dependent on vitamin-A, and she calls attention to the fact that it is a characteristic of squamous epithelium in general to become hyperplasic with deficiency of vitamin-A, and to be specially subject to infection. It is therefore possible that many of the cases of clinical parodontal disease have arisen in defective tissues already possessing the characteristics which progressive disease will accentuate. The effect on the hard tissues of lack of vitamin-D you are already familiar with, and it is obvious that they would favour the similar changes that occur in parodontal disease. Two facts stressed by James are of clinical interest. One is the continuity of the epithelial lining of the diseased pocket, and the other is the fact that the periodontal membrane is unaffected in the early stages of the disease. The former encourages treatment, and the latter makes one wonder what is the significance, if any, of the "thickened periodontal membrane" so constantly noted by radiologists in cases where there are few or no other signs of parodontal disease.

I am afraid no brilliant light has been thrown on the cause of this disease by experimental workers other than those I have mentioned. James regards the calculus below the gum-margins as the prime cause of irritation; Broderick [3] agrees, and goes further in believing that the cause of the calculus is an alkalosis leading to hypercalcification of the enamel from the saliva, and deposit of lime-salts as serumal calculus from the blood-serum. He emphasizes the well-known antagonism between dental caries and parodontal disease, and offers explanations of why the two may sometimes be coincident. The island of Tristan provides a light comedy element. The first examination of the inhabitants seemed to show that while dental caries was almost non-existent, parodontal disease was common, and Broderick quite naturally drew conclusions favourable to his views. But unfortunately the second examination by a well-trained dental surgeon showed that what had been taken for parodontal disease was no more than the superficial gingivitis due to calculus and diet which Broderick regards, I think rightly, as not parodontal disease at all. The fact is that parodontal disease in Tristan is as rare as caries, though gingivitis is common, and if the islanders did what they ought in support of Turner's views, there would be more than the 18% of teeth lost by the time the age-period of 46 to 55 was reached.

It is of course impossible now to discuss further the problem of the local versus the constitutional factor in parodontal disease. The probability is that, as in the case of dental caries, there is no real inconsistency between the two schools of thought. For my part, while being very far from denying that the origin of a certain type of case is spread from superficial gingivitis, I believe that the constitutional factor is of considerable importance. I am by no means certain that serumal calculus is present in some of the most typical cases of atrophic parodontal disease, and I venture to suggest that where it is present there is no proof that it is not a consequence, instead of a cause, of the morbid changes in the subgingival epithelium and corium.

The Dental Committee, with much to investigate, has been obliged to keep the work within circumscribed limits, that is to say, as closely as possible within the mouth, but the Committee felt that a detailed examination of the results of apical infection might prove valuable, and this was carried out by Mr. Arthur Bulleid. The results were interesting, if rather depressing, in that apparently the most infected regions exist where the root-treatment and filling have been most efficient. Granulomata he regards as an attempt to wall off the infection, and therein accords with Weston Price, but he considers that the walling off is only partially successful, because of the vascular connection, and is less satisfied with its effectiveness than Weston Price and Broderick, but after all we do not know anything about the interchange that takes place between the granuloma on the one hand and the surrounding

bone and systemic circulation on the other. I confess myself puzzled by the scant recognition which seems to be accorded to sclerosis as a method of isolation of an infected area. Sclerosis of the bone so closely resembles translucent areas and secondary dentine, both in origin and physical character, that I find it difficult to believe in its complete ineffectiveness.

Jeffery, following his experiments in penetration by cataphoresis, has investigated the sterilizing effects in root-canals by the same methods. The results are somewhat disappointing. He found, in conformity with other experimenters, that with currents of an intensity and for a period that would be clinically practicable it would only be possible to sterilize the root-canal and a portion of the dentine, and possibly a certain area beyond the apex. If it were possible effectively to sterilize the apical regions through the root-canal, a new phase in conservative dentistry would be opened up. Perhaps it need not be abandoned as definitely impossible. It has been the fashion in recent years to consider even small foci at apices as being more dangerous, or potentially dangerous, than sepsis from parodontal disease. I think perhaps this rests less on direct evidence than on the idea that a shut focus must be more likely to be carried by the blood-stream or lymphatics than an open one. This may be so as regards specific infection of other parts or organs, but in my own experience I think that all the cases in which I have seen a patient really ill and suffering from all the recognizable toxæmic signs and symptoms have been from a general sepsis of the mouth of parodontal origin, and I think that in these same cases the results of extraction and other treatment of the oral condition have confirmed the diagnosis. I put forward the hypothesis that a small septic focus may actually be of benefit to the individual. It is of course well known that freedom from a particular kind of infection for a period may render an individual highly susceptible, as for example the liability to the ordinary "cold" in those returned from winter sports in Switzerland. From time to time cases occur in which normally healthy people succumb to acute streptococcal poisoning following a slight injury, e.g. in gardening. It is at least arguable that a slight chronic focus of infection with some allied streptococcus might have saved them. I trust that I shall not be regarded as favouring the retention of septic foci generally, but I do suggest that considerations such as this may give us pause when adopting a generalized treatment based on knowledge of a limited kind, and perhaps of laboratory origin only.

I will refer briefly to one other entirely different kind of research which has engaged the attention of the Dental Committee. Ainsworth [1] showed in the course of his very careful and thorough examination of a large number of children that antero-posterior malocclusion, bilateral or unilateral, occurred in 23% of children. This is a very large figure and indicates some profound evolutionary change, or some defect in the development of the jaws, hereditary or environmental. It is clearly an important question for investigation. Keith and Campion, it may be remembered, did valuable work on the growth of the bones of the skull and face, and this was followed by Brash's admirable work on the growth of the jaws. Miss Smyth [25] has examined 1,200 carefully selected children between the ages of 8 and 14 with morphologically normal or ideal jaws; and Matthew Young has derived from her figures valuable statistics confirming the work and views of other observers and showing the correlation in growth in different dimensions. Friel and Shaw have each investigated the phenomena of close bite. Miss Bachrach's [2] investigation of twins, from which Matthew Young derived statistical results, showed quite definitely, in contra-distinction from caries, that there was a closer coincidence in the character of occlusion in identical twins than in fraternal twins. "In practically all cases where a more or less distinct irregularity of the teeth and arches was observed in one twin of the identical type, a similar defect was observed in the other twin of the pair." Oddly enough the resemblance was sometimes on

the same side of the mouth and sometimes on the opposite. Miss Still and Miss Elsa Bennett are now examining selected cases of definite types of abnormal malocclusion, and it is hoped that it may ultimately be possible to show in what respects the abnormal differ fundamentally from the normal, and perhaps to throw more light on their causation, and therefore on the principles of preventive and remedial treatment.

I cannot draw to a conclusion without thanking Mrs. Lindsay, who is always ready to assist workers in a good cause; she has provided me with an admirable summary of the work of the Dental Committee since its appointment, and has saved me much trouble in looking up articles and reprints.

I am conscious of having given you a mere sketch of the excellent research work done under the ægis of the Medical Research Council. In so doing I have referred to other work, but there is of course much that I have left untouched. I had two objects in view. One was, as I said at the beginning, to try to show how far the various researches were inter-related, and to what extent general or specific conclusions might be drawn from an aggregation of the parts; the other was to prove that the money had not been wasted. In the latter, at any rate, I hope I may claim to have been successful. Soon after the appointment of the Dental Committee the Dental Board decided to expend a considerable sum per annum on research, and in the case of clinical and pathological research to make use of the organization of the Medical Research Council and allocate an annual grant. Three-quarters of the money spent on dental research has therefore come from the dental profession. I believe that the results justify the expenditure. Even negative results are often of considerable value, but many of the positive results obtained are of value, and may prove to be of greater value still when taken in conjunction with further research.

And now what of the future? I doubt whether there is much more to be done in the histological or bacteriological aspects of either dental caries or parodontal disease. The dietetic and metabolic factors seem to be more alluring. A really thorough and scientific investigation of immune races, or regions, or individuals, might be productive. I believe that among European peoples the incidence of dental caries in Italy is very low. I understand that in India the incidence of caries is low and of parodontal disease high. It would be interesting to know how far the diet is lacking in vitamin-A or conducive to alkalosis. More discussion might be fruitful—when different people's ideas are rubbed together they sometimes emit sparks. Disputation, on the other hand, by which I mean the effort to prove that one person is completely right and another completely wrong, is almost always beside the point, and seems to me futile and wasteful of time and energy. Truth in scientific matters is established by work rather than argument.

When all is said and done, it seems to be tolerably certain that no easily applied panacea will be discovered for the prevention or cure of dental caries or parodontal disease. Both are intimately associated with our diet and methods of life, and prevention will be a political and social problem, and therefore of immense difficulty. While so much preventable disease remains unprevented we cannot expect very much from propaganda of dental prophylaxis based on incomplete knowledge. The time will doubtless come when physical perfection and good health are placed in the forefront of national requirements. When that time comes the people will be ready to grasp the truths that will enable them to repel many diseases at the site of entry, namely, the mouth. There has been much progress in public health due partly to an improved standard of living, and partly to the application of medical discovery by Government Departments. Our business is to inculcate the principles of prevention of dental disease, to strive, to work, and to think, until we know for a certainty how dental caries and parodontal disease can be banished. By then we shall have done our part. Education must do the rest.

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Section of Tropical Diseases and Parasitology

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DISCUSSION ON AVITAMINOSIS (B GROUP) IN TROPICAL AND TEMPERATE COUNTRIES

Dr. Harriette Chick: *The results of laboratory work on vitamin-B deficiency in relation to clinical experience.*—Of the group of dietary factors known as the B vitamins only two members are sufficiently well defined at present to merit consideration as of importance in clinical medicine. These are: (i) the anti-neuritic, anti-beriberi (more heat-labile) vitamin B_1; (ii) the anti-dermatitis, (?) anti-pellagra (relatively heat-stable) vitamin B_2, sometimes called vitamin G in the United States.

These two vitamins are both water soluble, vitamin B_1 being soluble also in alcohol even in strong concentration, vitamin B_2 less readily soluble, even in weak solutions. Vitamin B_2 is much the more heat-stable and can withstand high temperatures for long periods with relatively little destruction of activity, especially if the reaction is acid. These two vitamins have a similar, though not identical, distribution among natural foodstuffs, marked, however, by many quantitative differences (indicated in Table I by use of italics for the foodstuffs in question).

TABLE I.—DISTRIBUTION OF B VITAMINS (ROSCOE, 1931).

Vitamin B_1 (heat labile) anti-neuritic	Vitamin B_2 (heat stable), (?) anti-pellagra	Potency (dry wt.), yeast = 100
Yeast *Wheat embryo*	Yeast *Ox liver*	50—100
	Egg white Green leafy vegetables	20—40
Ox liver Green leafy vegetables Egg yolk	*Wheat embryo* Milk Meat Egg yolk	20—5
Milk Meat	Milled cereals	5
Egg white Milled cereals		0

Yeast is the richest known source of both vitamins. Ox liver is equally potent as regards vitamin B_2, but comparatively poor in vitamin B_1. The embryo and bran of cereal grains are rich sources of vitamin B_1 but poor in vitamin B_2; conversely the endosperm, while almost devoid of B_1, contains appreciable amounts of B_2. Egg white, devoid of B_1 and relatively rich in B_2, is the one foodstuff yet discovered which contains vitamin B_2 unaccompanied by vitamin B_1; no foodstuff is known of which the converse is true.

The results of deprivation of these two vitamins has been studied by feeding to animals "complete" synthetic diets in which only the one dietary factor is missing. In these experiments, the provision of the other member of the group has been the

chief difficulty. Vitamin B_1 is usually supplied as purified concentrates prepared from yeast or from the bran of cereals, vitamin B_2 as a strongly heated yeast extract or as a concentrate from egg white.

It is not easy to say how far the results of such observations are applicable to the facts of clinical experience with defective human dietaries, where a single uncomplicated deficiency must be a rare occurrence. The circumstances of climate, poverty, and racial custom, which are the cause of one dietary defect, are usually also the cause of others. It is also more usual for deficiencies to be partial rather than complete, so that a clear-cut syndrome of symptoms will be relatively uncommon.

Relation of vitamin B_1 (anti-neuritic) to human beriberi.

In the experimental animal, whether mammal or bird, vitamin-B_1 deficiency is marked by failure to grow, loss of appetite and weight, paralysis and muscular spasm leading to death if untreated, but yielding with dramatic swiftness to cure, if the missing vitamin is supplied.

This vitamin, the first to be detected, was discovered by Eijkman in Java in 1897, who observed among the poultry of the prison for which he acted as Medical Officer, symptoms reminiscent of those human inmates who suffered from beriberi. The fowls were fed on the surplus food scraps from the institution, and their diet was a replica of that of the prisoners, especially in its large content of highly milled rice. These facts led Eijkman to connect the two diseases with a similar ætiology and to pronounce in favour of a dietary theory for beriberi, at a period when current medical opinion favoured an infective one.

In many localities where beriberi is prevalent, the facts of its ætiology, prevention and cure have been found to be entirely consistent with the theory of causation by an unbalanced diet deficient in vitamin B_1, consisting too exclusively of a highly milled cereal, usually rice and, less frequently, wheat.

Such has been found true of beriberi outbreaks among the rice-eating populations of Java (Jansen and Donath 1926), the Philippine Islands (Albert 1915; Wells 1921), Siam (Theobald 1930) and Japan, and, in several of these localities, treatment is successfully carried out with vitamin B_1 concentrates from rice polishings specially prepared by the authorities for the purpose. In India, however, medical opinion is not wholly in accord with this view (McCarrison 1924; 1928; Megaw 1930) and it is possible that in this instance the causes may be more complicated and the deficiencies in diet less simple and less complete. Outbreaks of beriberi developing among wheat eaters, where conditions of poverty or climate have limited the diet too exclusively to white wheaten bread and flour, were reported among British soldiers serving in the Great War in the Near East, and more recently in Labrador (Aykroyd 1930) and Iceland (Kolka 1933).

TABLE II.—"DEFICIENCY" DISEASE ON UNBALANCED CEREAL DIETS.

Staple cereal in diet	Content of vitamin B_1	Content of vitamin B_2	Disease	Locality
Rice (milled and polished)	0	±	Beriberi	Philippine Islands Java Japan (India)
Wheat (white flour)	0	+	Beriberi	Newfoundland Iceland British Army (1914-1918)
Maize (whole grain)	++	+	Pellagra	United States N. Italy Roumania Egypt
,, (milled)	0	+	Pellagra	United States N. Italy Roumania Egypt

Relation of vitamin B_2 to human pellagra.

The experimental study of vitamin-B_2 deficiency has been made chiefly on young rats. When receiving synthetic diets lacking vitamin B_2 but complete in all other essentials (including the anti-neuritic vitamin B_1), these animals show failure to grow and frequently, but not invariably, develop a symmetrical dermatitis, which was considered by Goldberger and his associates (1926), who first described the condition, to be the analogue of human pellagra. When using dogs as experimental animals, a severe stomatitis, "black tongue," was developed, which resembled another phase of pellagra symptomatology.

In Table III, which is taken from a paper by Aykroyd and Roscoe (1929), a list of cereals and other food are placed in the order in which they have been found effective for prevention and cure: (*a*) of vitamin B_2 deficiency in rats; (*b*) of human pellagra in communities where the disease is endemic (Goldberger and others); (*c*) of "black tongue" in dogs. The striking similarity which is shown in the quantitative distribution among these foods of the dietary factor concerned in prevention of these three diseases leads irresistibly to the conclusion that they must be regarded as analogous. In consequence, the vitamin B_2 deficiency theory has been accepted by the Goldberger school and other authorities in the United States as affording an adequate explanation of the facts of the ætiology of pellagra.

TABLE III.—(AYKROYD AND ROSCOE 1929.)

ANIMAL	RAT	MAN	DOG
Material	Vitamin B_2 content	Pellagra-preventive, P-P, factor	Black-tongue preventive factor
Maize whole grain	Poor	Traditionally associated with pellagra in U.S.A. and Italy	No prevention, used in basal diet to produce the disease
Maize endosperm	Very poor		
Wheat, whole grain	Poor, but richer than maize	Associated with pellagra in U.S.A.	No prevention
Wheat, white flour	Very poor		

	Proportion in diet needed.		
	For good growth	For prevention of pellagra	For prevention of black tongue
Wheat embryo	15—30%	30%	31%
Fresh milk	5—10% solids	20% solids	250—300 c.c. (skim daily)
Lean meat	7—10% (dry wt.)	10% (dry wt.)	11% (dry wt.)
Dried yeast	1—3%	7%	5%
Liver	1—2% (dry wt.)	Extract curative	11% (dry wt.)
Egg yolk (dry)	7—15%	—	17%

A difficulty arises, however, in connexion with the almost universal association of epidemic pellagra with unbalanced diets containing maize as the staple cereal. Maize has not been found inferior to rice or wheat in content of vitamin B_2 (Aykroyd 1930), see Table II, and yet a population subsisting too exclusively on these latter cereals does not develop pellagra, but beriberi. Rice endosperm was found experimentally to be the poorest in vitamin B_2 of all the cereals tested, yet among rice-eaters pellagra, although not unknown, is somewhat of a rarity. These are points on which further clinical knowledge is badly needed.

Relation of B vitamins to other diseases.

Suggestions have been made connecting lack of B vitamins with many other disorders, as for example, the severe primary anæmias, sprue, œdema (as seen in "wet" beriberi, epidemic dropsy, or hunger œdema) and in acrodynia and other infantile disorders.

The evidence derived from clinical observations of the above diseases usually consists in the fact that good results have followed treatment with yeast, liver, liver extracts or other materials which are also rich in B vitamins. An error may easily be made in attributing to the action of the latter, effects which may be due to other important, as yet unknown, constituents of these highly complicated foodstuffs.

Anæmia.—The suggestion that vitamin-B_2 deficiency may be a factor in causation of *pernicious anæmia* has received much attention (Strauss and Castle 1932; Wills 1931, 1933) and will be discussed later by Dr. Lucy Wills.

Œdema.—The various forms of *epidemic dropsy*, to judge from the literature, would seem to have separate ætiologies. Good evidence was brought forward to show that the hunger œdema, common in Central Europe after the Great War, was due to a lack of protein food and to subsistence on diets low in calories and consisting too largely of root vegetables (Schittenhelm and Schlecht, 1919). In this connexion, however, it may be significant to note that the richest sources of B vitamins are found in foodstuffs also rich in protein of high nutritive value, e.g. yeast, liver, eggs. Outbreaks of œdema have also followed consumption of mouldy and deteriorated rice (Acton and Chopra 1925; Burnett 1933) and the condition is also typical of one common form of beriberi.

Acrodynia.—The association of vitamin-B deficiency with acrodynia (or "pink disease," or Swift's disease), the distressing malady of infants and young children characterized by intractable diarrhœa and typical skin lesions, has arisen from the good effects observed on this otherwise intractable condition by dietary treatment with foods rich in these vitamins. Some recent observations are summarized in Table IV. The effect of treatment with liver and liver extract was especially rapid and impressive in the observations of MacDonald (1933). Some authorities have seen in this infantile disorder the analogue of adult pellagra and it is significant that the two cases described by Mayerhofer (1930) had received a diet consisting almost exclusively of maize and that one case relapsed when maize was later introduced into the diet.

It is possible that other, less specific, departures from good health in infants and young children may be due to deficiency of B vitamins in the diet. In such cases the cause may only be recognized by observing the subsequent good effect when the diet is enriched with the vitamin in question. Thus Geiger and Rosenberg (1933) report a toxic condition prevalent in the spring among young infants in Jerusalem, which was cured by treatment with vitamin B_1; they observed a strictly analogous chain of events in their experimental animals. György and others (1933) have stated that a form of "infantile sprue," with anæmia, often occurs on a diet of goat's milk and yields to vitamin B_2 therapy, given as yeast extract and soup prepared from heart muscle, together with iron.

A connexion between vitamin-B deficiency and tongue atrophy—a characteristic symptom of sprue and of pernicious anæmia—has been stressed by several experimental workers (Hutter and Middleton 1933; Miller and Rhoads 1933) but, here again, it is probably erroneous, without further evidence, to attribute to the action of B vitamins the good results observed on treatment with liver or yeast.

TABLE IV.—ACRODYNIA IN INFANTS. (SWIFT'S DISEASE; PINK DISEASE.)

No. of cases	Age, years	Dietary cure	Observer
1	$5\frac{1}{12}$	Yeast + whole cereals	Nesbit (Texas), 1932
3	1 to 2	Yeast + "B" rich diet	McClendon (California), 1932, 1933
6	1 to $4\frac{1}{2}$	Liver or liver extract	Macdonald (Brisbane), 1933
4	2 to $7\frac{1}{2}$	"Good" diet (no maize)	Mayerhofer (Zagreb), 1930

Deficiency of B vitamins due to faulty absorption.

Vitamin deficiency may be caused either by actual lack in the diet or by faulty absorption from a diet of adequate vitamin content. Beriberi has not infrequently been observed in convalescent patients after dysentery and other disorders of the digestive system, as, for example, among the British troops in the Mediterranean area in the Great War (Willcox 1916). In such cases, however, the restricted diet would also be partly responsible. In pellagra, absence of gastric acidity is common (Mulholland and King 1933) and the appearance of the skin and other characteristic symptoms of the disease are usually preceded by chronic diarrhœa and digestive disturbance; a previous history of ulcerative conditions of the intestines was a constant feature in the great outbreak of pellagra among Turkish prisoners of war in Egypt immediately after the Great War (Searle and Stevenson 1920). Secondary pellagra, developing after tumours or surgical operations of the gastric and intestinal tract, is an analogous instance (Eusterman and O'Leary 1931) which is dealt with below by Dr. Levy Simpson.

Alcoholism and vitamin-B deficiency.

It has recently been suggested (Minot, Strauss and Cobb 1933) that alcoholic polyneuritis may be regarded as a deficiency disease, analogous to the neuritis of beriberi. The alcoholic addict tends to neglect other foods and can rarely be said to enjoy a good diet; in addition absorption is impaired in the damaged intestinal tract. Alcoholic pellagra is a frequent disease in the United States (Boggs and Padget 1932; Spies and DeWolf 1933), and the connexion between alcoholism and pellagra has been recognized in other countries, e.g. Roumania (Aykroyd 1933), in districts where pellagra is endemic. Here the possibility of a toxic factor in maize should not be overlooked in view of the facts (*a*) that alcoholic pellagra has become much more frequent in America during the prohibition period, in which illicit whisky ("moonshine") has been distilled principally from maize products, and (*b*) that the disease is almost unknown among alcoholic addicts in Europe, in districts where spirits are distilled from barley, or cereals other than maize.

Possible detoxicating action of B vitamins.

There are indications, derived alike from laboratory results and clinical experience, that vitamins may act as detoxicating agents for poisons either contained in the food as such, or derived therefrom by faulty metabolism in absence of adequate vitamin supply (Chick 1933). Such a theory would explain the facts concerning the incidence of several diseases whose origin is at present obscure. The conviction that some toxic factor underlies the symptoms of beriberi and pellagra is continually shown in the writings of clinicians dealing with these diseases. Eijkman (1897) conceived the action of the newly discovered anti-beriberi vitamin in yeast or rice polishings to be the neutralization of a poison developed during metabolism of a diet consisting too exclusively of highly milled rice. Mellanby (1925) has shown that cereals contain a "toxamin" which interferes with the correct metabolism of calcium and phosphorus, encouraging the development of rickets, and that the action of this toxamin can be neutralized by a sufficiency of the antirachitic vitamin D. The known facts concerning the ætiology of pellagra are in accord with a theory postulating a toxic substance present in maize and other pellagra-producing diets (or produced therefrom in metabolic processes in the body) for neutralization of which poison abundant vitamin B_2 is required (Chick 1933). Other instances are the effects of vitamin A in correcting the poisonous action of ergot (Mellanby 1931), and of yeast and liver in preventing the disorder produced in young rats receiving diets containing excessive amounts of egg white as protein (Boas-Fixsen 1927, 1931; Parsons 1931, 1933).

These and many other suggestions contained in this paper are at present hypothetical to a high degree. They are put forward in the hope that they may be found worthy of the attention of clinicians working in these fields of disease, and may stimulate not only an active discussion but further research on many problems which are very obscure at the present time.

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Professor R. A. Peters: The problem of vitamin B_1 and beriberi has a history of at least 40 years [1] and is so well worn that it may be thought somewhat impertinent to suggest that we do not yet know all about the therapeutic use of the vitamin. In one sense I think that this arises from our very familiarity with the subject. Vitamin B_1 has been used therapeutically for some time in the tropics [2], and in a reasonably pure state in Java, following the work of Jansen and Donath [3]. I wish to bring before you the significant new fact of the last year, that we can obtain to-day, with relative ease, really concentrated preparations of this vitamin [4]. Therefore the time has come to devote serious attention to investigation of possible conditions in which it may be of therapeutic value. For children in America vitamin-B_1 deficiency has been much considered. The view, often expressed, that there is no

vitamin-B_1 deficiency in temperate climates, such as ours, among adults, rests at present upon mere assertion, backed by the general clinical impression that beriberi does not occur. This is of course obvious in the gross sense. Actually the question cannot be answered until it has been shown whether patients suffering from any of the well-known clinical manifestations of beriberi are in fact influenced or otherwise by vitamin-B_1 therapy. There is a very thorough background of animal experiment to guide the clinical investigator in this field. It is well understood that controlled clinical experiments for instance in relation to œdema are difficult, but this provides no sufficient excuse for omission to perform them. It is only by the collective weight of clinical experience that this matter can be decided, because sufficient suitable cases for a decision are not likely to arise in the practice of any one individual. This is merely a statement of the obvious again, for which I plead as excuse a very strong belief that there do exist in this country cases of illness which may receive benefit from vitamin-B_1 therapy.

I propose to sketch briefly the present position of research upon the chemistry of the vitamin-B complex, directing my remarks mainly to vitamin B_1 and to emphasize the main features of animal experiments, including some discussion of the function of the vitamin, of its possible exhibition and its application.

The vitamin B complex has been divided by animal experimenters into some five or six entities [5]. Of these there is only time to mention vitamin B_1 and B_2, with regard to which the work is in some ways more advanced. Vitamin B_2 has been lately divided by the work of German investigators [6] into two fractions, one of which is believed to be identical with a pure crystalline substance, and the other to have some relation to vitamin B_4. The crystals are called flavines, and ovoflavine from egg white has the formula $C_{17}H_{20}N_4O_6$, is yellow with a green fluorescence, and is highly sensitive to light, a point which may be of importance in relation to the light sensitivity of pellagrins; if confirmed it is a striking development of the discovery of vitamin B_2 in egg white by Chick and colleagues [7]. The most interesting point to my mind is that some relation appears to hold between vitamin B_2 and the essential constituent of Warburg and Christian's new oxidizing enzyme [8]. Such a relation between vitamins and enzymes has often been sought before in vain. Vitamin B_1 is an entirely distinct entity from vitamin B_2. Impure crystalline preparations were first reached by Jansen and Donath [3] from rice polishings. In the last two years, crystals of greater purity have been reached in several laboratories [8, 9, 10, 11]; in at least two of these, including the author's laboratory at Oxford, from an original source of yeast. The remainder come from rice polishings. The hydrochloride of the base separates from acid absolute alcoholic solution in beautiful glistening plates. These become increasingly soluble as the proportion of water is increased. The crystals of different workers are alike in general properties, but still differ somewhat in potency, in chemical composition [10], and in ultra-violet absorption spectrum [12]. They contain sulphur, and those from rice polishings appear to agree exactly with the formula $C_{12}H_{18}O_2N_4S2HCl$. Some of the preparations from yeast contain more carbon and sulphur [13]. The most potent, and we can lay claim to possess these in Oxford, are curative to pigeons in doses of somewhat under 0·002 mg. per diem (approximately one international unit). At present my colleagues and myself think that the differences between preparations in different laboratories can probably be explained by the presence of varying admixtures of inactive and active vitamin. Activity appears to follow sulphur content, but it is not certain that pure vitamin B_1 has yet been reached.

Dr. Chick has referred to the symptoms shown by animals suffering from vitamin-B_1 deficiency. These have been well known since the earlier researches of Eijkmann Vedder and others (see also McCarrison [1]). During the last twelve years, my colleagues and I have handled a large number of pigeons, averaging during the last eight years 1,000 or more a year. The most striking things noticeable in my opinion

are as follows. The earliest symptom is always anorexia in the pigeon as in the dog (Cowgill and colleagues [14]). This is not specific for vitamin-B_1 deficiency. The most important specific symptom is of course the central nervous one, the so-called opisthotonus. With the onset of this go the disturbance of temperature regulation, a noticeable degree of blindness and certain well marked biochemical changes in the brain. The opisthotonus will clear up in some two hours with a large dose of vitamin by the mouth, in less when the vitamin is injected and within perhaps half an hour if it is injected into the cranium [15]. This is almost invariable, and precludes histological damage as its origin. The opisthotonus is *functional*. The insistence in the past upon pictures of histological change in avian polyneuritis has rather obscured this fact. We do occasionally see evidence of peripheral lesion, especially in young birds; there are cases of leg weakness which may not clear up for a month even when given vitamin B_1, but these are exceptional. Under our laboratory conditions, again, we do not usually see the beriberi columbarum of McCarrison, though we believe it to be present in a latent state, which Mr. Carter and I [15] [16] found may be developed by giving salt solution. Terrific retention of fluid may take place under these circumstances, amounting to some 50% of the body-weight; this may be completely cured by giving relatively very small amounts of active vitamin B_1. This requires study in relation to current theories of œdema and plasma proteins. To mention other significant points: pigeons have been given doses of upwards of 30-40 times the daily dose of vitamin B_1, without visible effects [17]; this is not surprising as excess is known to be excreted; but it is clear that no danger is likely to arise from moderate overdosage of the vitamin. There is much evidence to show that the amount of vitamin used bears some relation to the metabolic rate [14]. Lastly, in birds there is evidence of idiosyncrasy in response to a rice diet. I [15] believe that this will be very important if it can be shown that it applies to human needs. To some extent evidence already exists that this is so, because there are marked variations in the rate at which different individuals on the same diet get beriberi.

A complete understanding of the rôle of vitamin B_1 would be helpful in clinical work. There have been two main theories of its action, which have been pursued rather energetically in the past: (1) that B_1 is related to carbohydrate metabolism [18], and (2) that it is an oxidative factor [19]. Previous experiments in support of one or other have not proved convincing [20]. Recent work has shown that the key to this problem lay in a biochemical investigation of the avitaminous pigeon's brain tissue, and that both theories have an element of the truth. It has been definitely proved in the Biochemical Laboratory at Oxford that in absence of the vitamin there is an oxidative "lesion" in the avitaminous pigeon's brain [21], which is in some way connected with the metabolism of lactic acid, and therefore with carbohydrate. Absence of vitamin leads to increased lactic acid. The action of the crystalline vitamin upon the brain oxidases can be quantitatively investigated in vitro [22], and has been made the basis of a method of estimation of the vitamin. Minute amounts—0·00003% and less—are active. Now the depletion of vitamin in the brain as estimated by oxidative method, runs roughly parallel with the development of symptoms, especially marked is the lesion in the lower parts of the brain. Hence the symptoms arise as the result of the biochemical lesion which follows the lack of vitamin B_1. The alteration in the metabolism of the tissue is profound, and extends to the respiratory quotient, which changes from 0·95 to 0·75 approximately, a carbohydrate to a fat value [23]. Roughly speaking the avitaminous brain has the metabolism of tumour tissue [24]. Together with these specific effects in the brain tissue, there is apt to be a generalized increase of lactic acid in the blood and in the heart, as R. B. Fisher has shown [25]. His work is important because it builds a bridge between the bird and the human in beriberi. The Japanese workers Hayasaka and Inawashiro [26] have shown that

there is a defective removal of lactic acid from the blood of their patients. In the same field lie some recent observations in my laboratory, by Mr. R. H. S. Thompson [27], who finds indications that the pigeon's kidney may show failure in oxidations relieved by vitamin B_1 addition. If substantiated by further work, this will be of significance in explaining the latent œdema. In the bird it seems that lack of B_1 more readily affects the brain. In other animals, such as man, the œdema suggests that affection takes place elsewhere. It is unlikely that the underlying tissue biochemical lesion is not the same in the two cases.

Bearing the above laboratory work in mind, I wish to press for a proper trial of vitamin B_1 in clinical medicine [*cf.* 28]. To those engaged here in practical medicine, it would be presumption upon my part to suggest, as likely conditions will occur far more readily to you than to me. As an indication from the animal work and from the literature upon beriberi, we should look for its use, in the following conditions, at least: Loss of appetite; œdema; palpitation and breathlessness, especially when it can be shown that there is defective removal of blood lactic acid after exercise; neuritic conditions; painful muscles.

I think it hardly necessary to point out that it is not my view that all examples of these conditions are due to lack of this vitamin. This would be manifestly absurd. Particular cases will be so, and we cannot know which until we try. I had the privilege of being in Oxford in 1931 and 1932, in contact with two cases, which supplied most suggestive evidence, about which I hope that we shall hear in the discussion from Dr. Cope. There is also work from New Zealand by Carmalt Jones [29], to suggest that we are on the right track. May I emphasize that vitamin-B_1 treatment can do no harm, and that its effects are very rapid. If no change takes place with 500 to 1,000 units vitamin B_1 within two to four days, vitamin B_1 defect may be excluded, provided that absorptive conditions in the intestine are reasonably normal. The purer vitamin can, of course, be injected. It is almost certain that fevers and conditions of high metabolic rate, such as hyperthyroidism [30], should be watched for vitamin-B_1 deficiency, as a routine. I should also like to see clinical trials of the vitamin in convulsive nervous disorders; from the work upon pigeon's brain it is reasonable to think that some may respond to such treatment.

With regard to the concentrates which should be used for these tests: Dried yeast, marmite, and so on are excellent sources of the vitamin for ordinary use, but relatively large amounts of these would have to be given to supply 500 to 1,000 units B_1. This means the inclusion also of much inactive substance. I think that a patient should be able to get 1,000 units in 1 grm. or less of solid weight. If pure vitamin could be used, 2·0 mgm. would supply this amount. At present, there is still a high degree of technical chemical skill required to reach the crystalline vitamin. This will probably make it expensive, but there is no reason at all why commercial firms should not supply concentrates such as we make at Oxford, where we have worked up to the stage mentioned the vitamin from 400 cwt. of yeast in a week [4]. A detailed description of this method is now in print.

Before closing I should like to allude to a difficulty which I have found in the minds of some people with regard to bacteria. It has been said that because these synthesize vitamin B_1 in some cases, therefore the vitamin need not be supplied. The fallacies in this argument become clear upon realizing that (*a*) if the organisms contain the vitamin it cannot reach the individual, and (*b*) that there are bacteria which certainly can destroy it. In fact a prominent view of beriberi still held in some quarters is that bacteria contribute in some way to the final deficiency.

In conclusion the importance of this treatment for children and its great value to the expectant and nursing mother may be mentioned [31], but these facts and perusal of the literature relating to them would readily follow a conviction of the importance of the general thesis set forth.

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Mr. C. W. Carter: Among the pathological lesions which develop in pigeons fed upon an exclusive diet of polished rice must be included a condition of sinus bradycardia usually associated with bundle-block. The condition ranges in severity from an occasional missed ventricular beat to complete dissociation of rhythm of auricles and ventricles. After the commencement of a diet of polished rice the heart-block is established at an earlier date than the polyneuritis and head retraction. It is usually well developed within ten to fifteen days, whereas head retraction generally occurs between the twentieth to thirtieth day. Examination of electrocardiographic records reveals the fact that the P waves and ventricular complexes have normal contours. Section of both vagi or paralysis of vagal tone with atropine completely abolishes the block, whereas equal stimulation of the peripheral ends of the cut vagi of normal and avitaminous birds induces a similar degree of bradycardia in the two cases. These facts point to the conclusion that pigeon heart-block is nervous in origin, and due to an overaction of the vagal centres rather than to the influence of normal vagal tone upon a hypersensitive heart. In the rat Drury and Harris have shown that a sinus bradycardia without bundle-block develops as a sequel to feeding on a vitamin-B deficient diet. They find that, in contrast to what occurs in the pigeon, the condition is not abolished by vagal section.

It will be observed that the cardiac manifestations of beriberi in the pigeon and the rat differ from those seen in man. In the extensive literature on human beriberi

there is no evidence of heart-block even when electrocardiographic records have been made, and the usual accompaniment of the " wet " form of the disease is dilatation of the right side of the heart, with tachycardia and failure.

The fact that avian heart-block develops on a diet of polished rice and can be cured by an addition of whole yeast or wheat germ is indicative of a dietary deficiency, but this deficiency is definitely not in B_1.

Dr. Lucy Wills: Regarding vitamin-B deficiency in the anæmias: When the curative action of marmite in tropical macrocytic anæmia was first observed, it was thought possible that some part of the vitamin-B complex was the hæmopoietic factor. Castle also suggested that vitamin B_2 might be the extrinsic factor in true pernicious anæmia. Clinical trials showed that vitamins B_1, B_2 and B_4 had no hæmopoietic effect. The evidence points to this extrinsic factor being a protein breakdown product which is frequently associated with, but separable from, vitamin B_2.

Professor S. J. Cowell: There is a widespread belief that a partial deficiency of the vitamin-B complex may be largely responsible for the prevalence in this country of gastro-intestinal disorders, particularly chronic constipation. McCarrison (1919) drew attention to changes in the structure and functioning of the intestinal tract of birds fed on polished rice. He described atrophy of the muscular coats of the intestine, degeneration of Auerbach's plexus and the occurrence of mucous diarrhœa, and pointed out that the pathological changes were similar to those found in many cases of intestinal stasis. Since then many laboratory workers have interested themselves in the problem, but their results have been conflicting. Gross (1924) could not confirm in rats the histological picture described by McCarrison as resulting from vitamin-B deficiency in birds, but found a delay in the passage of fæces along the gut. Goudjonsson (1927), on the other hand, found an increased rate of movement of fæces along the gut of rats fed on diets deficient in vitamin B. Kon and Drummond (1927) could detect no difference in the rate of passage of a barium meal through the intestines of pigeons fed on diets deficient in vitamin B and those partially starved. Woollard (1927) could find no evidence of degeneration of sympathetic nerves in animals suffering from vitamin-B deficiency.

Loss of appetite is a remarkably constant symptom of vitamin-B deficiency in experimental animals. Cowgill has produced evidence that this loss of appetite is associated with atony and diminution of the normal rhythmic contractions of the stomach, but even this has been questioned. Smith (1927) published tracings of normal gastric contractions in a dog showing severe symptoms of vitamin-B deficiency. Cowgill and his colleagues (1930) mention this work, and produce further evidence in favour of their original view, but they state that " the decrease in gastric contractions is not due to any specific and direct effect of lack of vitamin B in the diet."

The evidence derived from laboratory animals is obviously still inconclusive, and while it seems clear that gastro-intestinal disturbances of one kind or another are liable to appear in animals suffering from vitamin-B deficiency no characteristic changes, with the possible exception of gastric atony, have been definitely traced to the deficiency.

Gruenfelder and his colleagues (1932) have recently described a type of acute gastro-enteritis in infants which often responds dramatically to injections of a vitamin-B concentrate, and they have still more recently published further evidence for considering the condition to be due primarily to vitamin-B deficiency.

The evidence for the view that chronic constipation is commonly due in this country to shortage of vitamin B is not altogether convincing. It is true that series

of cases have been reported from time to time in which obstinate constipation was relieved by giving preparations of cereal germ, bran or yeast. But it is sometimes forgotten that such preparations contain a great many other substances than members of the vitamin-B complex. As Professor Peters has already suggested, there does not appear to be much chance of defining the exact part played by deficiency of the vitamin-B factors in the production of gastro-intestinal disorders until pure preparations of the factors are available for clinical trial.

Dr. S. Levy Simpson said that the condition known as secondary pellagra, first described by O'Leary in America (1926) and not hitherto reported on in this country, was clinically identical with pellagra, but thought to be secondary to primary gastro-intestinal lesions or malfunction. These were as follows: gastrectomy, gastro-jejunostomy, chronic gastritis, syphilitic gastritis, alcohol gastritis, carcinoma of the stomach, jejunostomy, duodenal feeding, stenosis of the small intestine, stenosis of the large intestine, carcinoma of the rectum, chronic diarrhœa and idiopathic steatorrhœa.

An identical list could be put forward for those comparatively rare examples of "secondary" pernicious anæmia and megalocytic hyperchromic anæmias. Why in the one case the anti-pellagra factor (B_2) and in the other case the anti-anæmic factor should manifest its deficiency it was difficult to say. It was of interest to note that although these two factors were definitely not identical, yet they were present together in substances that were beneficial in pellagra and some hyperchromic anæmias, namely, marmite and certain liver extracts. O'Leary ascribed secondary pellagra to the fact that the intestinal lesion necessitated a poor diet deficient in vitamin B_2. Thaysen referred to the exclusion of gastric digestion, and Turner to changes in intestinal bacterial flora. In his (Dr. Levy Simpson's) opinion other factors should also be considered: (1) deficient absorption, (2) destruction of vitamin B_2 by alkalin gastric contents.

[Dr. Levy Simpson briefly described a case of secondary pellagra in a woman, aged 46, who had had gastrectomy three years ago for duodenal ulcer. The skin lesion disappeared rapidly on a concentrated pure vitamin B_2 preparation made from egg white by Miss Harriette Chick at the Lister Institute. A coincident secondary hypochromic anæmia reponded to iron therapy. Biopsy of skin on the forearm showed hyperkeratosis and pigmentation in the basal layer of the epidermis—a microscopical picture identical with that of a typical case of asylum pellagra seen recently. Sections of skin taken by Professor Ledingham from Miss Chick's rats (fed on a vitamin B_2 deficiency diet) showed a similar microscopic picture, but no pigment.]

Dr. C. C. Ungley summarized the results obtained in an investigation as to the nature of the factor in yeast efficient in the treatment of pernicious anæmia.[1] These were as follows:—

(i) The negligible result obtained from the administration of vitamin-B_2 concentrates in a patient with Addisonian pernicious anæmia, who subsequently responded well to an extract of autolyzed yeast, suggested that potency for blood regeneration in this type of anæmia is not proportional to vitamin-B_2 potency as tested in rats.

(ii) A factor influencing blood regeneration in Addisonian pernicious anæmia appears to be present in the 65% alcohol-soluble fraction of fresh brewer's yeast, and yeast from the same batch subjected to autolysis before extraction has not shown any noticeable increase in potency.

[1] This work was performed with the assistance of a part-time grant from the Medical Research Council.

(iii) In an endeavour to avoid contact with traces of intrinsic factor possibly present in the gastric juice of cases of Addisonian pernicious anæmia, yeast products effective for blood regeneration when given orally have been administered by other routes. In spite of the negative results so far obtained from parenteral administration, there is as yet insufficient evidence for the conclusion that the effect of yeast in this disease is dependent solely upon the activation of extrinsic factor by traces of intrinsic factor in the patients' gastric juice.

(iv) No extract of yeast, autolyzed or otherwise, has proved sufficiently reliable to be of value for the routine treatment of Addisonian pernicious anæmia. It is conceivable that satisfactory results may ultimately be obtained with more purified fractions, by the use of which it will be possible to administer extracts derived from several pounds of yeast daily.

Dr. Margaret Balfour said that she had been much impressed when in India, with the frequency of premature births, especially in Bombay, and thought that possibly deficiency of vitamin B_1 was in some way responsible, especially as in many cases no clinical symptom could account for the prematurity. In the course of an inquiry carried on by Dr. Lucy Wills it was found that the mothers who had given birth to premature children were living on a diet deficient in vitamin B. Later the diets of mothers who had given birth to premature children were investigated in North and South India. In the North the diet is rich in vitamin B (wheat, dâl, vegetables and milk); in the South it is relatively poor (mainly polished rice, and small quantities of dâl and vegetables). There was some evidence that women of the North accustomed to the first-named diet, when they changed to a rice dietary, were apt to be prematurely delivered.

The diets of 290 pregnant women in Bombay, beginning from the sixth month until delivery, were studied, and 12% had premature deliveries. The average calorie content was 1,500, and wheat and millet were the main source of vitamin B_1. When 50% of the calories were derived from polished rice there were 19% of premature births, but when the same number of calories were obtained from wheat or millet there were premature deliveries. The incidence of premature birth varied with the amount of wheat taken. When the total cases were divided into four groups whose daily diet included respectively more than 8 oz. of wheat, between 4 to 8 oz., less than 4 oz., or none at all, the respective incidence of prematurity was 3%, 6%, 15% and 20%.

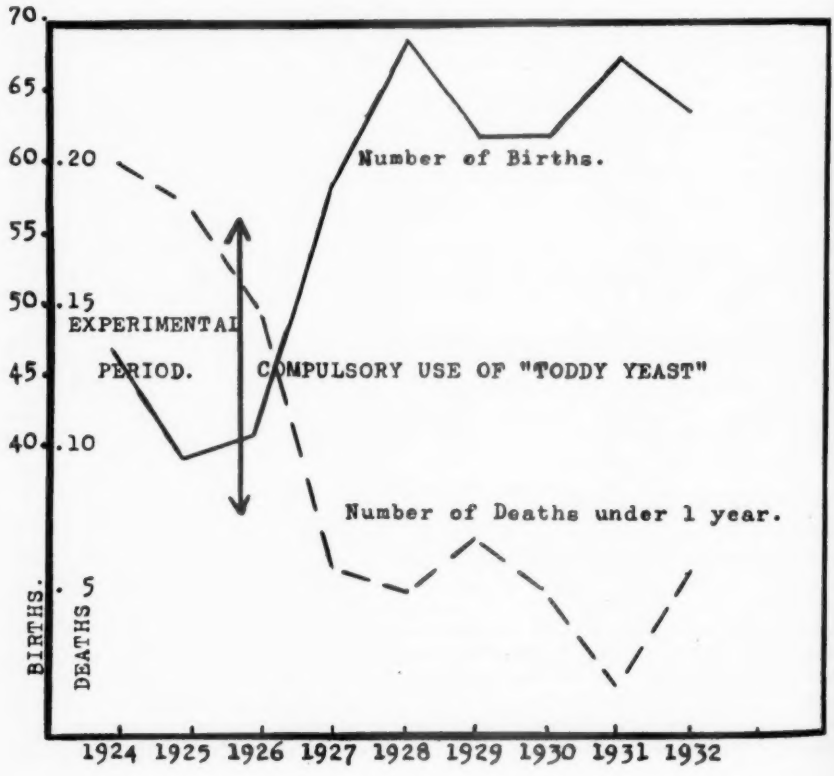
Other workers have shown that if a mother rat is deprived of vitamin B_1 during lactation, the growth of the young will be retarded or will stop altogether. It is therefore not unlikely that vitamin B_1 may be important in pregnancy, and that a lack of it may influence the fœtus or cause thinning of the decidual membranes. If the growth of the fœtus is in this way retarded, the question why so many Indian babies are born small and feeble may be answered.

Dr. W. Cramer said he was surprised that Professor Cowell should have thrown doubt on the relation of vitamin B to gastro-intestinal functions. The most obvious post-mortem appearance in a rat kept for some time on a vitamin-B-deficient diet was an enormously dilated stomach, always completely filled with food; this indicated some interference with the mechanism of emptying the stomach. Other naked-eye appearances were the atrophy of the intestinal wall and of the lymphoid tissue throughout the body, including the Peyer's patches. His (the speaker's) own observations agreed with the statement that the passage of food through the small intestine was not delayed, and that strips of intestine immersed in Ringer's solution contracted spontaneously, although, owing to the atrophic condition of the intestinal wall, these contractions were less powerful than those of normal strips.

The large intestine was always filled with impacted fæces. The fact that white bread caused constipation, which was relieved by a change to wholemeal bread, was known to clinicians long before vitamins were discovered. That this was not due to the mechanical action of the bran was shown by the fact that the constipation was also relieved by germ bread or by yeast which did not contain bran, but were rich in vitamin B. That the absorption of food was impaired by the absence of vitamin B had been shown by Dr. J. C. Mottram and himself in 1922.

Dr. G. Bray said that some years ago he had written a paper on vitamin-B deficiency in infants (*Trans. Roy. Soc. Trop. Med. and Hyg.*, 1928, xxii, 9). At Nauru, Central Pacific, 45% of the infants born in a year died before their first birthday, and he had shown that this was due entirely to a deficiency of vitamin B in the mother's diet. Vitamin B was added to the mother's diet and every infant from birth was given each day a teaspoonful and a half of "toddy yeast" (the yeast which grows in the sap of the coconut spathe). As a result the infantile death-rate dropped from 450 per 1,000 births to 92 per 1,000 within a year, and this figure had been maintained during the five succeeding years, while the birth-rate had increased by 60%. Also during the last six years there had not been one case of maternal mortality in an average of 65 births per year.

These facts are shown in the following graph :—



Dr. C. L. Cope referred to a case of glomerulonephritis with severe "nephrotische Einschlag" in a youth aged 19, in whom severe œdema of 50 to 60 lb. was resistant for eighteen months to the usual treatments with diuretics, high protein diet, intensive alkali treatment, &c. This youth was given by mouth large doses of an extract of autolyzed yeast rich in the vitamin-B complex. On the day following the first administration of the vitamin, the urine output rose from its previous average of 75 oz. per day to about 120 oz., at which level it was maintained for several weeks, whilst the body-weight fell by from 5 to 7 lb. per week until only a trace of œdema remained. Coincident with loss of œdema was a rapid fall in the previously high plasma-cholesterol, and a rise in the albumin fraction of the plasma proteins, the globulin remaining constant. In three out of five such cases treated with large doses of B complex a marked diuresis has ensued, with subsidence of the œdema. It is suggested that in long standing œdema of nephrotic type a condition of B deficiency may tend to develop as a secondary complication and may help to aggravate the general metabolic disorder and the œdematous state.

The President said that, speaking as a clinician, the picture one saw when watching cases of beriberi or pellagra in their acute phases, was one of acute intoxication. He had some difficulty (and he had said the same thing for many years) in reconciling this positive side of the picture with the negativistic theory postulated when one spoke of the avitaminoses or deficiency diseases. He had always believed that there must be a positive factor in the production of the clinical manifestations, a factor which, perhaps, only came into play in the absence of a vitamin. This possible other side of the subject had been rather overshadowed by the work on vitamins.

He was glad that Professor Peters had laid stress on the fact that the symptoms in the B_1-deficiency disease in experimental pigeons were functional and that they reacted within an hour to treatment. The term "polyneuritis" was a misnomer, the gross histological changes which had been described had nothing to do with the symptoms. He had seen the same head-retraction in pellagra as Professor Peters had described in pigeons; it was a symptom possibly indicating the approach of the convulsions which might occur in acute pellagra. This and other toxic symptoms might clear up with a dose of castor oil!

He had been interested to hear of those cases of animals in which symptoms failed to appear on avitaminic diets, failure ascribed by Professor Peters to idiosyncrasy. Much light might be shed on the question if the nature of this idiosyncrasy were known. He thought a closer study of these unusual cases of pellagra associated with gross organic disease of the gastro-intestinal tract, with alcoholism, &c., might help considerably in the elucidation of the problem.

JOINT DISCUSSION No. 1

Section of Psychiatry, and Section of Therapeutics and Pharmacology

Chairman—Dr. E. MAPOTHER (President of the Section of Psychiatry)

[*December* 12, 1933]

DISCUSSION ON THE USES AND DANGERS OF HYPNOTIC DRUGS OTHER THAN ALKALOIDS

Sir William Willcox : At the British Medical Association Annual Meeting at Brighton, in July 1913, I opened a discussion in the Section of Therapeutics and Pharmacology, on "The use and abuse of hypnotics."

Since 1913 the chief advances in our knowledge of hypnotic drugs have been (1) The discovery and addition to the list of hypnotic drugs of many new derivatives of the barbituric acid series; (2) the introduction of a number of drugs other than alkaloids for purposes of basal anæsthesia.

A hypnotic drug may be defined as a drug or combination of drugs which produces sleep resembling natural sleep.

Insomnia is due to many causes, e.g. pain; psychical causes; organic diseases of the nervous system; toxic causes, such as microbic infections, auto-intoxication, drug addiction and chemical poisons; disorders or diseases of one or more of the various systems such as the gastro-intestinal, cardiovascular, respiratory, genito-urinary, or endocrine.

Treatment.—In the treatment of insomnia the first step is to elucidate its cause. and it will be generally agreed that the use of hypnotic drugs should be resorted to only when other general methods of treatment have failed to bring about a satisfactory result or are likely to be of inadequate effect.

The choice of the hypnotic for a particular case will largely depend on the cause of the insomnia; for example, after a severe abdominal operation one would probably select a drug not belonging to this series at all (e.g. a hypodermic injection of morphine) in order to induce sleep on the night after the operation.

Drugs of vegetable origin will be excluded from consideration.

Classification.—The classification of hypnotic drugs on a purely chemical or pharmacological basis is difficult and unsatisfactory, so that an attempt will be made to classify them on chemical and clinical lines.

Hypnotic Drugs of Low Toxicity are:—

The inorganic bromides (e.g. of potassium, sodium, ammonium, calcium and strontium). They are mild hypnotics suitable for certain nervous cases and may be given in full doses up to 30 grains at night.

Alcohol in certain cases in prescribed amount.

Phenazone and its derivatives such as pyramidon.

Aceto-salicylic acid and salicylate derivatives.

Phenacetin, etc., etc.

Combinations of these with other hypnotics, such as opium preparations or codeine, are often effective.

Hypnotic Drugs of Varying Degree of Toxicity are:—

THE ALCOHOL CHLORAL GROUP.

Chloral, dose 10 to 20 grains; an effective rapidly acting and safe hypnotic. In full doses it is depressant to the heart and respiratory functions. If used continuously it may have a toxic action on the liver and cause toxic jaundice, also it may give rise to addiction. This hypnotic has undeservedly fallen into disuse.

Chloralamide (Chloral Formidum BP), dose 15 to 45 grains. It is a safe and mild hypnotic. Like chloral it is incompatible with alkalies which cause decomposition. When used on successive nights the hypnotic effect is apt to diminish so that this drug is used much less than formerly.

Other chloral derivatives which are not commonly used at the present time:—

Butyl chloral, dose 5 to 20 grains. Useful in the insomnia of neuralgia.

Chloralose, dose 3 to 10 grains. A compound of chloral and glucose. It is not free from toxic effects such as excitement, tremors, and cardiac depression. It is rarely used.

Chlorbutol, also known as "chloretone"; dose 5 to 20 grains; more toxic and less effective as a hypnotic than chloral.

Hypnal, a compound of chloral and antipyrin; dose 5 to 15 grains; is rarely used.

Dormiol, a compound of chloral and amylene hydrate; dose 5 to 40 minims; is rarely used.

Ural, a compound of chloral and urethane; dose 15 to 45 grains; a dangerous and uncertain hypnotic.

Isopral is tri-chlor-isopropyl alcohol. Dose 10 to 30 grains. It has fallen into disuse owing to its toxic effects in causing cardiac depression and gastric disturbance.

Bromal, dose 2 to 5 grains; is more toxic and less certain in hypnotic action than chloral.

Paraldehyde, dose ½ to 2 drachms. A useful and safe hypnotic. It has an unpleasant taste. Is soluble in water 1 in 9. It is contra-indicated in gastric and respiratory diseases. Its repeated use may cause toxic liver effects and give rise to addiction (paper by Dr. Carver, 1933, Society for the Study of Inebriety).

Amylene hydrate, dose 30 to 60 minims. It acts like paraldehyde, but is less certain and more toxic.

Aponal, a compound of amylene hydrate and urea; dose 10 to 20 grains. Is said to be a safe hypnotic and less unpleasant to take than amylene hydrate. It is rarely used.

Hedonal is isomeric with aponal; dose 10 to 20 grains. Is an uncertain hypnotic.

Neuronal, di-ethyl-bromide acetamide, dose 5 to 20 grains. It is a powerful hypnotic, but has toxic effects on the heart and alimentary system, and causes skin rashes. It has fallen into disuse.

Avertin is tri-brom-ethyl alcohol. It has been used extensively as a basal anæsthetic and is administered rectally. The dose recommended by the introducers is (0·1 gramme) 1¾ to 1¼ grains per kilogram body-weight of the patient, but there are many conditions which would demand a considerably smaller dose than this. Care and experience are required to decide on the suitable dosage for basal anæsthesia. It may cause prolonged coma, or toxic liver effects such as jaundice in susceptible patients.

THE UREA GROUP.

Urethane.—Ethyl carbamate, dose 15 to 30 grains. A mild and safe hypnotic. Is suitable for children.

Aleudrin.—Di-chlor-isopropyl-carbamate. Dose 10 to 30 grains. Is little used.

Uradal or *adalin* is brom-di-ethyl acetyl urea. Dose 5 to 15 grains. It is a sedative as well as hypnotic. It is a useful and safe hypnotic. I have met with no cases of addiction or toxic effects from its use.

Uvaleral or *bromural* or *dormigene* is a mono-brom-isovaleryl urea; dose 5 to 10 grains. Is a useful and safe hypnotic.

Somnosal is a proprietary preparation composed of a mixture of bromural and dimethyl-amido-phenyl-methyl-iso-pyrazalon. Dose 5 to 10 grains. Is a mild and safe hypnotic.

Sulphone Group.

Sulphonal is dimethyl-methane-di-ethyl sulphone. Dose 10 to 30 grains.
Trional is methyl-sulphonal, dose 10 to 20 grains.
Tetronal is ethyl sulphonal, dose 10 to 20 grains.

These hypnotics are only slightly soluble in water. They are very slowly absorbed and their action thereby may be much delayed. They are powerful hypnotics, but owing to their delayed and uncertain action are less used than formerly. They have been much used in asylum practice.

Dangers from this group are: (1) A cumulative effect owing to delayed absorption if the drug has been taken in repeated daily dose, when coma may develop unexpectedly. There are many recorded cases of drug addiction.

(2) Repeated use of the drugs may lead to troublesome skin rashes of urticarial or erythematous type often associated with marked prurigo. Vesicular and bullous eruptions and purpura have been observed.

(3) Hæmatoporphyrinuria is a common but not constant symptom.

Mental depression leading to suicidal tendency and the taking of an overdose.

Subjective and objective toxic effects on the nervous system such as hallucinations, slurred and thick speech, diplopia, squint, ataxy, drowsiness and stupor.

Overdosage may be followed by deep coma lasting over a prolonged period (several days), and during this period there is danger of the development of basal broncho-pneumonia which is usually fatal. In these cases the drug has been found in the cerebrospinal fluid. An extensor plantar reflex is common during the stage of coma.

Fatal dose.—Death has occurred after one dose of 30 grains in a neurasthenic woman. Probably an average minimum fatal dose for an adult is about 75 grains, but recovery has occurred after very much larger doses. Several deaths have followed the daily use of from 10 to 20 grains over periods of from two to twelve months.

The Barbituric Acid Group.

Barbitone or *veronal* is di-ethyl-barbituric acid.
Sodium barbitone or *medinal* is the sodium salt of barbitone.
Proponyl is dipropyl barbituric acid, and
Neonal or *soneryl* is N. butyl-ethyl-barbituric acid.
Dial is di-allyl-barbituric acid.
Phenobarbitone or *luminal* is di-phenyl-barbituric acid, and
Sodium luminal is its sodium salt.
Phanadorm is cyclo-hexenyl-ethyl barbituric acid.
Evipan is N. methyl-cyclo-hexenyl-methyl barbituric acid, and
Sodium evipan is its sodium salt.
Pento-barbitone is ethyl-methyl-butyl-barbituric acid, and its sodium salt is *Nembutal*.
Ipral is calcium ethyl iso-propyl-barbituric acid.
Allonal is a combination of allyl-isopropyl barbituric acid with amidopyrin (causes a reddish brown colour to the urine from the amidopyrin present).

Veramon, a combination of veronal with amidopyrin (causes a reddish brown colour in urine).

Gardenal is phenyl-ethyl barbituric acid.

Cibalgin is a combination of dial and amidopyrin (causes a reddish brown colour to urine).

Somnifaine is a combination of allyl-isopropyl barbituric acid and veronal.

Sodium hebaral is the sodium salt of hexyl-ethyl-barbituric acid—it is given by the mouth for insomnia.

Beatol is a proprietary preparation said to be a mixture of veronal with extracts of valerian and jusquiame.

Quadronox is a proprietary preparation said to contain 80% veronal, with phenacetin, phenazone, etc. (urine may be coloured reddish brown from the phenazone present).

Amytal is iso-amyl-ethyl barbituric acid, and the sodium salt is used for intravenous purposes (anæsthesia).

Pernocton is 2.butyl-bromethyl barbituric acid. The sodium salt is used intravenously.

A considerable number of other preparations containing barbituric acid derivatives is on the market.

The addition of alkyl or aryl radicles of higher molecular weight than ethyl adds to the toxicity of the substance, thus luminal, dial, proponal, gardenal, soneryl and nembutal are all more toxic than veronal.

Launoy and Contière, taking veronal as unity, have found that the relative toxicity for dial is 3·1, for soneryl 4·7, for amytal 10·1, and for nembutal 10·1.

The combination of a barbituric acid compound with an analgesic drug such as amidopyrin, phenacetin, etc., occurs in veramon, allonal, cibalgin, and quadronox appears to me to be dangerous since the barbituric acid compound is much more toxic than the analgesic drug, and this may lead to an overdosage of the barbiturate when the preparation is taken in large doses to relieve pain.

Uses.—The barbituric acid derivatives are perhaps the most commonly used hypnotics at the present day. When taken by the mouth they are quickly absorbed and within an hour or so after a clinical dose sleep usually ensues.

After a single therapeutic dose a period of sleep lasting from six to twelve hours usually occurs, without unpleasant after-effects. There is more certainty of action than with most of the other hypnotics. These are the reasons for the popularity of this group of hypnotics.

All of the above group of drugs have been used for hypnotic purposes. When one remembers that the toxicity of the derivative increases with the substitution of larger radicles than ethyl, it is probably safer to use for hypnotic purposes barbitone or its sodium salt than the more complex derivatives.

Many of the group mentioned have been used for basal anæsthesia. Those which are most commonly used at the present time for this purpose are nembutal, pernocton, amytal and evipan.

Dangers from this group.—As with other poisons, if taken on an empty stomach and in solution, the effect is more rapid and intense. The taking of alcohol with the drug seems to increase the toxic effect (recent case of quadronox poisoning).

(*I*) *Idiosyncrasy.*—(A) Natural. Some persons have a natural increased susceptibility to all drugs, often there is present a highly strung nervous temperament, and there is a history of abnormally excessive reaction to medicinal preparations.

(B) Acquired is shown by :—

(1) *Allergy.*—Allergic patients are often abnormally susceptible, e.g., a history of asthma, urticarial attacks, angio-neurotic œdema, etc., are an indication of this state.

(2) *Defective renal function.*—The usual symptoms of acute or chronic nephritis may be present, but a chronic cystitis accompanied by a latent pyelitis will greatly increase the susceptibility, even if the blood urea is little above the normal.

(3) *Defective liver function*, e.g., a history of cirrhosis or tendency to jaundice or to attacks of acidosis may be present as an indication.

(4) *Hyperthyroidism.*—This greatly increases the susceptibility to these drugs, for example, nembutal is dangerous as a basal anæsthetic.

(5) *Myocardial disease* as shown by tachycardia and other signs of cardiac disease.

(6) *Alcoholic addicts.* In them the action is uncertain.

(7) *Glycosuria* is evidence of defective pancreatic or hepatic function and is an indication of likely idiosyncrasy.

(8) *Toxic condition.*—The prolonged toxic effects of some existing disease greatly enhance the susceptibility of the patient to this group of drugs especially the basal anæsthetics.

(*II*) *Subjective and objective toxic effects on the central nervous system.*—Idiosyncrasy may lead to symptoms of acute or subacute poisoning from a normal full dose, e.g., I have seen prolonged coma, suppression of urine and broncho-pneumonia follow a normal dose by mouth of two capsules (three grains) of nembutal.

The repeated use of therapeutic doses not uncommonly causes some symptoms such as mental depression, drowsiness, visual hallucinations, vertigo, ataxic gait, thick and indistinct speech (anarthric) diplopia, squint, nystagmus, difficulty of protrusion of the tongue, paralysis of a limb, facial paralysis, tremors of the hands, etc.

Albuminuria occurs sometimes, hæmatoporphyrinuria rarely. A reddish-brown-coloured urine is present where a phenazone derivative is combined with the barbituric acid compound. Skin rashes of an urticarial, erythematous or bullous type may occur.

The symptoms from chronic or subacute poisoning very closely resemble those of organic nervous diseases such as encephalitis lethargica, bulbar paralysis, cerebellar disease, general paralysis of the insane, alcoholism, peripheral neuritis, etc.

In 1927 a paper was read before this Section by Dr. F. A. Pickworth[1] in which it was shown by animal experiments that actual degenerative changes occurred in the nerve-cells after the prolonged administration of barbituric acid compounds. This work had been carried out by the late Sir Frederick Mott in conjunction with Dr. Pickworth, and I have no doubt as to its accuracy. There is therefore a pathological basis for the toxic nervous symptoms which are observed clinically.

(*III*) *Cumulative effect.*—In healthy persons barbituric acid compounds are fairly rapidly excreted and cumulation does not readily occur. Where repeated doses are taken there is an accumulation of the toxic effects as shown by the objective nervous symptoms mentioned. In these cases discontinuance of the drug for a few days leads to disappearance of the symptoms. I have seen toxic jaundice follow the daily taking of one grain of luminal for over a year.

(*IV*) *Tolerance.*—Only a slight degree of tolerance to this group of drugs is established even after long use. It is for this reason that a moderate overdose is usually followed by severe symptoms.

(*V*) *Habit formation.*—I have seen a large number of cases in which a definite craving for the drug has arisen after repeated daily administration, and the daily use of the drug has been continued in spite of strong medical advice to the contrary.

Addiction to the barbituric acid group of drugs differs from morphine and heroin addiction in that sudden discontinuance is not followed by severe withdrawal symptoms.

1 *Proceedings*, 1927, xx, 1486 (Sect. Therap., 20).

(*VI*) *Risk of fatality from suicide.*—I have been greatly impressed by this. Persons who have been taking the barbituric acid derivatives daily for a long period very commonly take a large overdose when they are faced with mental stress and worry and often death results thereby. I have met with cases in which suicide has been effected by taking an overdose of lysol or other poison. The danger of overdosage must always be borne in mind in the case of persons taking barbituric acid drugs in repeated daily doses; it is a very real danger.

A recent example of this occurred in the case of a well-known physician whom I saw, in which a large overdose of veramon was taken with fatal result.

Illustrative Cases.

(1) F., aged 35. Domestic worry. Had been taking two tablets of veronal nightly for several weeks. Greatly depressed; tremors of facial muscles; ataxic gait; visual hallucinations. Symptoms completely cleared up after five weeks.

(2) M., aged 34. In institution for treatment for chronic alcoholism. Had been given allonal, four tablets nightly for several weeks. No alcohol taken while in institution. He developed thick and indistinct speech, diplopia and ataxic gait. Wassermann reaction negative. Symptoms cleared up on discontinuance of allonal.

(3) M., aged 45. Suffering from acute rheumatic fibrositis. Had been given medinal, 10 grains, for six nights. On examination drowsy, bilateral ptosis. Speech indistinct and thick. Diplopia on looking to left. Mental condition somewhat confused. Has been seeing objects which were non-existent (visual hallucinations). No history of alcoholism or evidence of syphilis. The symptoms completely cleared up in a week after discontinuance of the medinal.

(4) M., aged 60. History of epilepsy. Had taken luminal 1½ grains daily for eighteen months. On examination: jaundice (present for fourteen days), some abdominal pain in in hepatic region. Drowsy for three days. Sick several times daily the last three days. Liver slightly enlarged. This patient was obviously in a condition of commencing acute yellow atrophy.

On discontinuance of the luminal and with intensive treatment with alkalies and glucose the symptoms cleared up after a few days.

(5) F. M., aged 60, doctor's wife, said to have taken a few (? 6) tablets of dial. On examination four hours afterwards deep coma, loss of conjunctival reflexes. Stomach washed out. Strong coffee given. Colon washed out.

Consciousness recovered within fourteen hours when delirium and restlessness occurred. Good recovery.

(6) F., aged 65. Operation for gall-stones and intestinal obstruction. Nembutal given intravenously for anæsthesia. On the day after operation defective articulation; two days after operation confused defective articulation. Suppression of urine after operation. Death occurred four days after operation.

(7) M., aged 55. Suffering from chronic streptococcal toxæmia. On December 23, 1932, two capsules of nembutal were given. A deep sleep lasting twenty-eight hours occurred. December 26, 1932: one capsule of nembutal given at noon. On December 27, 1932, at 4.30 a.m., one capsule of nembutal given and at 1 p.m. one capsule of nembutal given (by mouth). Coma followed in two hours. At 6 p.m., T. 101°; R. 40; 8 p.m., T. 103°; at 9.45 p.m., T. 102°, R. 60. Dulness over right lower lobe, deficient air entry and crepitation.

11.30 p.m., lumbar puncture, 30 c.c. of fluid drawn off. December 28th, 1932, 6 p.m., recovery of consciousness. Temperature normal. Lung signs beginning to clear up. Retention of urine occurred for four days and some suppression (58 oz. of urine passed in four days by catheter). Good recovery occurred.

(8) F., aged 89. Operation for vesico-vaginal fistula which had been present for nine months. Nembutal, one capsule, given the night before operation. Two capsules nembutal given an hour before operation the following morning. Gas and oxygen given also for anæsthesia.

After operation deep coma supervened with all the signs of acute barbituric acid poisoning. Typical pneumonia occurred; death resulted fifty-one hours after the operation. Blood-urea 57 mgm. per 100 c.c. eighteen hours before death.

This was clearly a case of nembutal poisoning, the idiosyncrasy being due to the toxic effects of the genito-urinary infection on the heart and kidneys.

The need for care in the use of hypnotics is obvious, particularly when there are any of the danger signs above mentioned.

In psychical cases an obsession of insomnia sometimes occurs and ordinary therapeutic doses seem to have little or no effect. It is probable that such cases would be better treated by psycho-therapeutic measures than by drugs.

Basal anæsthesia.—The need for care in dosage with the drugs used for this purpose cannot be too strongly emphasized. If a therapeutic dose (which in a susceptible person may be an overdose) be given, either intravenously or by mouth, it cannot be withdrawn, since absorption is rapid and one has to combat the full effect of the toxic symptoms.

Where any of the dangers mentioned are present, if a basal anæsthetic is used at all, a minimum dose should be given and full anæsthesia obtained by a general anæsthetic such as gas-and-oxygen or ether.

In a recent case in which avertin was desired by the patient, it was decided, after consultation, to give a half dose, since glycosuria and myocardial weakness were present. Some of the solution was returned after rectal administration and probably only about a third of the normal dose was absorbed.

This patient was able to talk up to the time of the abdominal operation which was performed under gas-and-oxygen and ether. After recovery from the operation the patient stated that he had no recollection of the events preceding the operation and a full amnesia was attained with the small dose.

In cases in which there is a possibility of danger it appears to me that if a basal anæsthesia is used, a reduced dose should be given which would effect amnesia without causing complete loss of consciousness.

Conclusions.

In prescribing hypnotics it is wise to select one, or a combination, of the less toxic type of drugs whose action is well known. I have been so impressed by their toxic effects that I never prescribe any of the barbituric acid group of drugs or of the sulphonal group.

Need for control of the prescription of hypnotic drugs of toxic properties.—These drugs should only be obtained on the prescription from the medical adviser, and the prescription should be retained by the pharmacist and not repeated, except on medical authority and signature.

The total quantity ordered on a prescription should be well under a possible fatal dose.

Legislation regarding the sale of poisons is under consideration as a result of the recent Poisons and Pharmacy Act which was passed this year (1933).

A close co-operation between the medical profession and those practising pharmacy is essential if dangers from hypnotic drugs are to be avoided.

Dr. F. L. Golla: I think that we shall all agree with Sir William Willcox that, when we attempt to produce sleep or quietude in an excited organism, no single type of hypnotic medication is universally applicable and it may be worth while to attempt, however briefly, a physiological analysis of the mechanisms involved in the production of sleep, or at any rate of relative quiescence. That our knowledge is still extremely scanty is hardly to be wondered at when we realize how very recent are any systematic investigations on this subject. Its long history of comparative neglect is the result of the undue exaltation of cortical function that has proved an

omnipresent stumbling-block in psychiatry. We have forgotten what was perfectly well appreciated in Aristotelian psychology, namely, that the body and nervous system act as a whole.

Only within the last few years has it been accepted that a complex centre exists in the tuber-infundibular region, disturbance of whose functions is capable of producing sleep, though as long ago as 1890 Munthner connected the then existing epidemic of sleepy sickness with lesions in the periventricular grey matter.

The clinical and pathological evidence that lesions in this region cause pathological sleep is very considerable and rests on the observation of cases of neoplasms, tuberculomata and encephalitic lesions affecting the tuber-infundibular region. Experimentally Mehes produced sleep in rabbits and dogs by means of electrolytic lesions made by needles in the diencephalon. Demole, basing his experiments on the alleged diminution of the calcium content of the blood in sleep, found that injection of a dilute calcium solution into the infundibular region caused intense somnolescence. Similar results attended the injection of magnesium sulphate. Injection of potassium chloride caused general restlessness and hyperexcitability. Veronal injections produced deep sleep.

These experiments have been confirmed by other authors; Berggren and Moberg, Marinesco, Sager and Kreindler obtained similar results and further noted that ergotamine injections in the same region caused sleep. Whilst Brunelli finds that acetyl choline causes a condition of agitation, similar experiments by Marinesco yielded first agitation and then somnolescence as a result of acetyl choline injection. Hess produced sleep by exciting the median diencephalic area with feeble interrupted currents, whilst strong currents produced a condition of agitation. Marinesco and his pupils found that anodic polarization of the infundibulo-ventricular region tends to produce sleep whilst cathodic polarization is without effect. In view of all these data many writers have proclaimed the existence of a diencephalic sleep centre. It is difficult to understand how such an extraordinary inverted interpretation of the facts has been arrived at.

If the pathological evidence and the effect of destructive lesions mean anything, they mean that the activity of a centre whose function it is to maintain a condition of general excitability of the central nervous system has been destroyed, and were it necessary to use either of the terms we should talk rather of a waking centre than a sleep centre. Nor do the results obtained by injection and electrical stimulation point to any other conclusion. In the infundibular region are situated the central ganglia of the autonomic system governing heat production, water and salt metabolism, cardiac and vasomotor equilibrium.

All that we know of sleep points to an abeyance of the katabolic activity associated with the sympathetic system and an increase of the anabolic activity associated with the parasympathetic system. The sleep-producing effects of ergotamine are consonant with paralysis of the sympathetic centres. The reciprocal actions of weak and strong currents in inhibiting and stimulating the centre find analogies in the physiology of the vegetative nervous system without even having to go back to Richet's celebrated experiment on the inhibition and excitation of the claw muscle of Astacus. Anodic polarization diminishes cell excitability, whilst kathodic polarization heightens it, and as we have just seen, sleep is conditioned by anodic polarization. Potassium increases nervous excitability, calcium and magnesium diminish it.

Now, if we accept the body of histochemical evidence of Keeser and others, it is precisely on this group of vegetative nuclei that the barbiturates exert their chief action. Thus, when we attempt to produce sleep by pushing these hypnotics, a powerfully depressant drug is called on to exert its activity on a group of nerve-centres which constitute a veritable *nœud vital* governing general cell metabolism. The dangers inherent in this therapy are obvious.

We cannot, of course, consider this diencephalic centre subserving excitability as autonomous. It is reasonable to suppose that its excitability is maintained by a constant stream of impulses arriving from the sensory end-organs via the thalamus, from the subcortical mechanism for protective and emotional movements, from the proprioceptive system, and above all from directly or indirectly initiated cortical activity. Appropriate destructive lesions of the thalamus, the injection of calcium or the barbiturates, produce, generally, sleep or a condition of somnolescence. It would appear that only one non-alkaloid acts selectively on the thalamus. The possibility of diminishing painful stimuli without, as far as can be judged, markedly affecting cortical activity would appear to rest with the salicylates. These thus act in a secondary sense as hypnotics.

Let us now turn to those motor mechanisms that are especially interesting to psychiatrists, inasmuch as their hyperactivity is to a great extent responsible for the restlessness of many agitated conditions. We are dealing with a primitive subcortical mechanism actuated on the one hand by sensory impulses relayed from the thalamus, and on the other serving as the effector system for the stream of emotive impulses activated by cortical excitability. From the activity of these terminal ganglia of the parapyramidal motor system, stimulation of the diencephalic centres results. In addition the diencephalic activity again stimulates the cortex, thus establishing a vicious circle. To discuss the pharmacological attack on these mechanisms would lead me into the forbidden territory of the alkaloids—at any rate in no other way can I explain the magical effect of hyoscine in acute mania or some experiments of my own, when a temporary quiescence and even sleep was obtained in cases of agitated melancholia by exhibition of bulbocapnine, a drug which in moderate doses acts solely on the parapyramidal system.

The experience of most of those who have seen much of neurotic behaviour is that a sufficiently lengthy stimulation of a subordinate mechanism by cortical hyperactivity may lead to the lower centres exhibiting a functional hypertrophy long after the original stimulating cause has ceased to act. In the treatment of insomnia due to such a residual and persistent symptom, it is obviously bad practice to weaken the cortical inhibitory powers by a cortical hypnotic when a direct attack can be made on the hypertrophied mechanism.

If we now consider the treatment of excitatory states depending on hyperactivity of the cortex alone it is clear that there is no indication for using drugs such as the barbiturates in doses that can affect the vegetative diencephalic system when sufficient cortical depression may be obtained by drugs such as the bromine compounds which have no effect in ordinary doses on the lower centres. Here again, in the study of selective action of drugs on different aspects of cortical function, we are in contact with an almost unexplored problem of great complexity. Cortical hyper-excitability cannot be considered as necessarily involving the whole cortical system. The specific action of certain hypnotics on the motor cortex is a good example. Many other drugs which have a generalized action in depressing cortical activity, and others which have a specialized action on the sensory cortex, possess only a very feeble depressant power on the motor cortex. Nor have we attained the knowledge that will allow us to predict from chemical constitution the probable effect of any drug on any one cortical mechanism. Witness the different actions of such nearly allied drugs as diallylmalonylurea and phenylethylbarbituric acid on the motor cortex. As a disbeliever in the conventional cerebral localization I hold strongly that the cortex acts as a whole, and that no anomaly of function in one respect will fail to affect in varying degrees all forms of cortical activity; but I do not conceive that such a view precludes the recognition of a variability in definite systemic functions when considered physiologically rather than anatomically.

An apparent reversal of function may characterize the employment of a cortical

hypnotic. Blachwenn and others have observed that inaccessible catatonics, on recovering from amytal anæsthesia, become active and accessible, whilst still retaining their delusions. That this is really only a release of function due to a localized action of the attenuated hypnotic was shown by Lindman who observed that precisely the same effect could be obtained by the continuous administration of small doses of amytal. When the same doses were given to normal observers they reported a sensation of general *bien-être* and expansiveness and a desire to converse with the world at large on their most intimate affairs. Similar probably was the experience of William James with ether, when he found himself able to resolve all antinomies in a species of Hegelian absolute under its influence. If there be one contribution more urgently needed than another it is that which psychiatrists could make by an analysis of the introspections of trained subjects under the influence of hypnotics.

Of the more strictly pharmacological problems I must leave others to speak. I am glad to say that we have with us Professor Alfred Meyer whose work on the histological changes induced by hypnotics is known to all, though I am afraid that we shall find him rather a destructive critic.

Finally, while we shall all agree with the very wise cautions that we have received from Sir William Willcox on the rash recourse to hypnotic therapy, there is one class of cases in which not to take risks is to fail in our duty. Not all of us have been exposed to a great sorrow, but those who have will have some inkling of the unendurable torture that makes the sufferer from acute melancholia desire death at all costs. These unfortunate people should be relieved without regard to the risks involved—which, on any reckoning, are not so very great. I believe, however, that the failures and dangers of hypnotic treatment will be greatly diminished when increased knowledge of the specific action of the drugs and a more thorough-going analysis of the different nervous mechanisms involved enable us to prescribe the right hypnotic for the particular symptoms.

Professor J. A. Gunn: Sleep may be regarded as a rhythmic condition of depressed excitability of the brain, and insomnia as an absence of this depression or a failure of its rhythm. From the practical purposes of drug treatment, insomnia may be regarded as due to one, or a combination, of two causes.

(*a*) Abnormal afferent stimuli which maintain the excitability of the brain at a time when its depression is due;

(*b*) Increased excitability of the brain cells.

To treat every case of insomnia by the administration of a hypnotic is just as irrational as to treat every case of cough by administration of morphine. If insomnia is due to abnormal afferent stimuli from the senses or autonomic system, the rational treatment is to remove these stimuli if possible. Increased excitability of the brain may be congenital or acquired. There are great individual variations in the capacity for sleep, as there are in other qualities of the central nervous system. There are brains which are easily kept awake. There are children who, though perfectly healthy, from infancy sleep far less than other equally healthy children and this endowment of wakefulness may, for good or ill, persist through life. This has not necessarily anything to do with intellectual capacity. Increased excitability of the brain may also be artificially produced, e.g. by caffeine or possibly by nicotine. It may be secondary to high blood-pressure, as in the insomnia produced by ephedrine. In the latter conditions treatment, if needed, is obvious. Excitable brains are prone to need hypnotics. There are, however, brains of normal excitability, that may be kept awake by such abnormal cerebral stimuli as "worry." It is possibly for this condition that bromides are especially valuable.

Such a classification of insomnia suggests, in the first place, obvious reasons for

combining an analgesic and a hypnotic. Aspirin or phenacetin, by diminishing afferent stimuli of pain or discomfort, may produce sleep alone or will diminish the dose needed of a drug that acts as a cerebral depressant. Experiments on normal animals do not give a true estimate of the value of such a combination in insomnia due to pain. A small dose of morphine, only sufficient to act as an analgesic may, when combined with a cerebral sedative like chloral, be more effective in producing sleep and safer than a large dose of either alone. It also suggests reasons in some cases for combining different hypnotics which act at different points, e.g. the familiar combination of chloral and bromides.

The numerous hypnotics which act by depressing the brain are usually grouped according to their chemical relationships or their speed and duration of action, it being rather assumed that their sites of action are identical. Gross differences in site of action are realized, e.g. between hyoscine and chloral, or possibly between luminal and veronal. It is on this point that our knowledge is most scanty, and it is only if such differences exist and are utilized that there can be any justification for the ever-increasing number of hypnotics. If we always knew more narrowly the "site" of the insomnia and the site of action of hypnotics, it would be easier to find the right key for the lock. Some experience of the action of hypnotics on the lower animals shows that there are finer differences in the action on the brain (apart from other pharmacological differences) shown by drugs which are at the present time merely labelled "hypnotics." It may be that in time we shall come to use them with more physiological discrimination. Even now therapeutics would gain by a more accurate knowledge of fewer hypnotics.

One factor ought to be better controlled, viz. dosage. Little attention is paid to whether a man weighs 10 or 15 stone; though a difference of 50 per cent. in the dose may make all the difference in the effect produced. The time may come when we shall reckon all doses of active drugs per unit (e.g. stone or kilogram) of body-weight. With hypnotics as with other remedies we are not nearly accurate enough in our dosage and we have scarcely progressed in this respect in the last century.

I can refer to only one or two points concerning the dangers of hypnotics. In the first place I think it would be worth while for someone to analyse the published accounts of cases of poisoning by hypnotics in Man with a view to ascertaining whether these effects throw any light upon the precise site of action on the central nervous system. Secondly, in regard to tolerance produced by repeated doses of hypnotics, it is known that different tissues in the same animal develop different degrees of tolerance to any particular hypnotic. We are apt to estimate tolerance by the effect on the nervous system, forgetting that a tolerance so narrowly judged may overlook the obscured absence of tolerance on the part of such organs as the liver or kidney. Thirdly, we must take cognizance of the great increase in recent years of cases of accidental and suicidal poisoning with hypnotics, especially of the barbituric series. To quote from a recent set of statistics (which could be paralleled in most countries) there were admitted into the hospitals in Budapest, from 1909-14, 35 cases of veronal poisoning, in 1932 there were admitted into one hospital of that city 87 cases. Even that increase did not represent the increase in poisoning by this group, because luminal had appeared on the list. In 1923 there was in this hospital one case of luminal and 23 of veronal poisoning, in 1932 there were 80 of luminal and 87 of veronal poisoning. One potent factor in this increase of poisoning is the prescription of tablets. They are too easily obtained and in too numerous doses. They are too portable and too facile in use. People accustomed to take relatively innocuous drugs such as aspirin in tablet form are apt to regard tablets as safe.

With many drugs there is a wide margin between the therapeutic and toxic doses. Nevertheless it is idle to expect that a drug which has sufficient pharmaco-

logical activity adequately to depress the brain will not fail, in larger doses, to spread its actions. The history, especially of hypnotics, reveals a procession of drugs which have been introduced, sometimes by academic pharmacologists, more often by drug manufacturers, with the claims that they are "therapeutically active" but "non-toxic," and not a single example has entirely lived up to this twofold recommendation.

Dr. P. K. McCowan: Hypnotic drugs owe their action to certain chemical groupings in their molecules, and for convenience of description I am making use of a classification, according to their chemical composition, into the aldehyde, the halogen, the sulphone and alkyl, and the urea groups.

Aldehyde group.—Paraldehyde is probably the safest hypnotic which we possess. As an aldehyde it is a cardiac and respiratory stimulant and can be used with comparative safety in any condition calling for a hypnotic. The great objection to this drug is its taste and smell of course, and its excretion by the lungs accounts for the prolongation of its odour for the day following its use. Cases of poisoning from paraldehyde are extremely rare, and the only cases which have come under my personal notice have been where patients have been given from one to three ounces of pure paraldehyde in mistake for an ordinary draught. Such patients have slept for periods varying from 24 to 48 hours, but, with appropriate treatment, have made uneventful recoveries.

Halogen group.—*Chloral hydrate* is an extremely useful hypnotic, which is less used since the introduction of the much advertised barbiturates. As it is a cardiac and respiratory depressant, it has to be used with caution in the debilitated and old, but for general use it is one of our safest hypnotics. Outside India, addiction to chloral is rare, probably on account of its unpleasant taste, its irritant effects on the gastro-intestinal tract, its liability to produce rashes, and the absence of a preliminary stage of excitement and stimulation. Of all drugs of addiction, it is, however, the most liable to produce pathological changes in the organs.

Sulphone-alkyl group.—The two common hypnotics here are sulphonal and trional. Owing to past abuse, sulphonal has of late fallen into an unmerited disrepute. If its tendency to accumulation is remembered and guarded against, it is a useful and safe hypnotic, with no untoward action on the heart or respiration. Its prolonged use should be avoided, and, personally, I never use it for longer periods than a week.

I find it particularly useful in acute exacerbations of excitement in chronic psychoses; from 20 to 30 grains three times daily for three days will frequently succeed in cutting short such acute attacks.

Trional acts more quickly than sulphonal, and is rather less accumulative; but most results obtained by this drug can probably be obtained as well, if not better, with one or other of the barbiturates.

Urea group.—Here are included the innumerable drugs of the barbituric acid derivatives. Since the introduction of veronal in 1903, new drugs of this series are continually being offered to the profession with claims that they are more powerful, more rapidly excreted, and less toxic than their predecessors; and especially of late years has this been the case.

The following are a few of these drugs, arranged in order of their hypnotic strength: *nembutal, avertin, dial, allonal, veronal, phanadorn, pernocton, luminal, amytal, barbital.* The rate of excretion of the drug is important, in that delayed excretion increases the danger of post-hypnotic effects and cumulative action.

However, clinical experience largely confirms the animal experiments of Weiss and many others, which show that the main action of all these drugs is highly similar. The chief differences between them lie in the intensity of the excitement they sometimes cause before and after sleep, and in the duration of their action.

They all act as sedatives, analgesics and hypnotics, depending on the amount administered. If the hypnotic dose is expressed in percentages of the minimal lethal dose, then the latitude between hypnotic and fatal dose is found to be practically the same for all of them. It is herein that lies their chief danger—namely, that the optimum hypnotic dose is roughly 50% of the lethal, which, of course, allows little margin for such things as idiosyncrasy and the presence of contra-indications.

Recent publications from the Maudsley Hospital and the Boston Psychopathic Institute report very favourably on the use of nembutal in psychiatric practice; and my own experience of this drug is in accordance with the results obtained at these two hospitals.

Nembutal can be used either as a sedative or hypnotic, the usual dose being 3 to 6 grains. It acts quickly and is excreted fairly rapidly; there is no appreciable tendency to tolerance and it is markedly free from unpleasant after-effects. It is a powerful drug, certain in its action, and, used intelligently, can be fairly described as a comparatively safe hypnotic. While it is quite permissible to try out any new drug, I think it is advisable to familiarize one's self with one particular drug. By so doing, one certainly obtains the best results, as one comes to know exactly what dose to give in a particular case if a certain result is desired, and also one appreciates better the onset of any untoward symptoms. I think that practical experience of the drug used is of more importance in the results obtained than is the specific action of the particular drug chosen.

As regards the barbiturates in general, there is a consensus of opinion among those who have used these drugs extensively, that as sedatives and occasional hypnotics they are eminently safe, and I should like to go on to show that, given in conjunction with glucose and insulin, they are also safe in prolonged narcosis. Work by Quastel in the Cardiff City Mental Hospital Laboratories has shown that these barbiturates inhibit the oxidation of glucose and lactic acid by the brain. This deprives the brain of what is recognized as one of its chief sources of energy, and, therefore, interferes with the functional activity of the brain-cells.

That this inhibition of brain oxidation is the *modus operandi* of narcotics is suggested, among other things, by the work at Cardiff, where we have demonstrated a close parallelism between hypnotic activity and this inhibition of glucose and lactic acid oxidation. The stronger the hypnotic power of the barbiturate, the greater its inhibitive power on these brain oxidations.

This discovery of the interference with the carbohydrate metabolism of the brain, together with clinical evidence that ketonuria is frequently present in prolonged narcosis, suggested that the carbohydrate metabolism of the liver might be similarly upset. Quastel proved that this was, in fact, the case, liver tissue in the presence of narcotics showing similar inhibition of its oxidative powers. These facts justify the conclusion that, while certain of the toxic symptoms of the barbiturates (such as rashes and albuminuria) are due to peripheral causes, and others (such as disturbances of co-ordination, pyrexia, some of the fall of blood-pressure and epileptiform seizures) are due to the drug's action on the central nervous system, others are due to the disturbed carbohydrate metabolism. This disturbance sets up a condition of ketosis, with such symptoms as ketonuria, vomiting, cyanosis and coma. The cardiac collapse, which is one of the chief dangers in prolonged narcosis, is also associated with a carbohydrate upset, the heart muscle being apparently affected in a similar way to the brain and the liver.

These facts give the clue to a method for preventing or treating toxic symptoms arising in prolonged narcosis, for, by the administration of glucose and insulin, we are able to combat the drug's action on the liver and cardiac muscle. Glucose itself is useless, for it requires the co-operation of insulin for its proper metabolism in the liver; hence, the inhibitive action of a narcotic on carbohydrate metabolism in the liver requires the presence of insulin to diminish this inhibitive influence. In

the presence of insulin, the functional activity of the liver cells need not be appreciably affected. Presumably this is also the case with cardiac muscle, which physiological experiment has shown requires the co-operation of insulin for its maximum activity. On the other hand, the brain takes its glucose from the blood-stream and utilizes it independently of insulin, so that the presence of insulin in no way interferes with the narcotic action of the drug.

Certain it is that in Cardiff a series of over 50 cases have been treated in this way with a most striking diminution of toxic symptoms, as compared with a similar series treated with somnifaine alone. At first we did not exhibit the glucose and insulin until the onset of toxic symptoms, but we have found the results much better since we began to give the glucose and insulin from the commencement of the course.

We now find it very exceptional to have to discontinue treatment before the full course of fourteen days has been given. Toxic symptoms when present are mild, and at the end of the treatment the patient has none of the toxic look previously associated with this treatment. The drug we have found most generally useful is somnifaine, administered intramuscularly. A complete course extends over fourteen days, and consists of two or three daily injections of 2 c.c. somnifaine. With each dose of somnifaine is given 10 units of insulin, and care is taken that the patient drinks a plentiful supply of glucose. Other drugs which we have used, but found less satisfactory, are dial, veronal, pernocton and amytal.

Following on the above work, I have been investigating of late the carbohydrate metabolism of patients taking sedatives in the usual way, and have been interested to find that a certain proportion of them sooner or later show ketonuria or glycosuria, symptoms which can be quickly cleared up by the use of glucose and insulin. I would suggest, therefore, that it is advisable in using sedatives or hypnotics in any case where special care is necessary to administer glucose and insulin simultaneously with the drug. The cases I have in mind are those of the toxic exhaustive psychoses and patients with exhaustive symptoms associated with mania, melancholia or one of the neuroses. I would further suggest that glucose and insulin might well be given as a routine measure when a hypnotic is used prior to surgical anæsthesia.

Addiction in the barbiturates.—The danger of this does not appear to be any greater in the case of the barbiturates than with other hypnotics. Most of the reported cases are with veronal, and it is found that the cases of acute poisoning usually occur in manic-depressives, while chronic addiction is practically confined to psychopaths, many of whom are alcoholic, and some of whom are morphine addicts. These drugs are not classed as dangerous drugs, so that they are quite easily obtainable. This tendency to addiction in psychopaths must be kept in mind in giving prescriptions for these drugs.

I have no special knowledge of the use of barbiturates in midwifery, but I do feel that my clinical and biochemical knowledge of the action of these drugs justifies me in expressing an opinion on the controversial subject of their use previous to surgical anæsthesia.

These drugs are admirably suited, both in theory and practice, for this purpose; and it seems to me that, if the published reports of inquests following the use of nembutal and other barbiturates are reliable, there is a marked tendency in certain quarters to exaggerate the toxicity of these drugs.

These reports suggest a failure to apportion correctly (1) the toxic effect of the barbiturate; (2) the effects of prolonged general anæsthesia, and (3) the shock of surgical operation.

The matter would be of little importance but for the official source of the opinion, which, I fear, will tend to prevent the use of these drugs in cases for which they are eminently suitable. Expressed differently, one might say that, with such views prevalent, the chief danger in the use of the newer barbiturates is not to the person taking the drug but to the one prescribing it!

Finally, sedative and hypnotic drugs should be used as a last and not as a first resort. In mental hospital practice, the giving of sedatives and hypnotics can be very much reduced by the use of such measures as occupational therapy and hydrotherapy. An investigation by the Board of Control into this question showed that in those hospitals where such measures were extensively practised, the amount of sedative and hypnotic drugs used was considerably less than in other hospitals.

Sir James Purves-Stewart: I wish to reinforce Sir William Willcox's remarks on the occasional unexpected toxic effects of barbituric compounds in ordinary doses. I will quote three illustrative cases :—

(I) A lady, aged 60, complained of unsteadiness of the legs, coming on rapidly two months after an attack of herpes zoster.

Physical examination showed well-marked signs of spinal-cord affection, including ataxia of the legs, loss of vibration-sense in the lower limbs, absent ankle-jerks, and extensor plantar responses. The cerebrospinal fluid was normal with a negative Wassermann reaction, a normal cell-count and negative globulin and gold reactions. The blood-count also proved normal.

She herself had recently noticed some difficulty in spelling, together with dysphasic symptoms, such as omitting a word, now and then, when writing or speaking. Moreover, she once sat down and addressed a letter to herself, instead of to her correspondent.

On inquiry I found that she had been taking 10 grains of medinal daily for several years, without medical advice.

On withdrawal of the medinal, all the abnormal physical signs, both spinal and cerebral, cleared up within a couple of weeks.

(II) A young officer, aged 33, who had suffered from bouts of dipsomania for thirteen or fourteen years, married an American heiress. She was a strong prohibitionist and insisted that her husband should undertake prolonged and systematic treatment in a special institution for alcoholism.

Six weeks after his admission to this home, during which time he had no alcohol whatever, and had been having atropine and strychnine in progressively increasing doses, he rapidly developed vertigo and a staggering gait. He began to fall on the golf-course and when getting out of his bath. One day he came up to lunch at his London club, in company with his medical adviser. Although he had had no alcohol for many weeks, his club friends noticed him to be indistinct in speech and staggering in his gait. They promptly diagnosed these as due to alcohol, much to the patient's indignation.

Further inquiry elicited that for the last three weeks he had been taking four tablets of allonal daily (a combination of barbiturate with pyramidon), this being an ordinary dose for sleeplessness.

On withdrawal of the allonal, his symptoms cleared up completely.

(III) A woman, aged 47, about the time of the menopause, had been suffering for two years from chronic high blood-pressure with headaches and insomnia.

She then rapidly developed unsteadiness of gait, tingling and numbness of the left upper limb, and defective sensation in the feet. She also complained of failing memory, with slowness of speech, thought and action, of which she herself was perfectly conscious. After seven weeks of these symptoms, when I first saw her, I found that she was intelligent and coherent, but slightly dazed. There was paralysis of upward movement of both eyes. The optic discs and other cranial nerves were normal. She walked feebly and unsteadily in a cerebellar fashion, clutching at the furniture. There was generalized blunting of sensation all over the body to all varieties of stimuli. The tendon reflexes and plantar responses were normal.

On inquiry I found that for twelve months she had been taking 15 grains of medinal every night. Analysis of the urine showed the presence of medinal; none was found in the cerebrospinal fluid.

On withdrawal of the medinal medication, all the symptoms—cerebral, quadrigeminal, and cerebellar—promptly cleared up within a couple of weeks.

In none of the cases which I have quoted did the patient volunteer a history of drug-taking. It had to be inquired for, and this increased the difficulties of diagnosis.

It would seem, therefore, that whilst in full doses these narcotic drugs exercise their widespread toxic effect on the whole brain, from cortex down to medulla, an effect which may sometimes be fatal, in smaller and repeated doses they may have a selective action upon special groups of nerve-cells, e.g. in the cortex, mid-brain, cerebellum, and even medulla. Why are there such differences in the clinical symptoms? Probably because of individual variations in the vulnerability of different nuclei in the central nervous system.

Dr. R. D. Gillespie: My contribution is concerned with the possible dangers of the barbiturate group of drugs, and especially with any possible relationship between therapeutic doses and lethal effect. The belief that exists in some quarters that the barbiturates are dangerous implies one or other or all of the following three assumptions: (1) That they are dangerous in therapeutic doses, that is, that the margin between the therapeutic dose and the lethal one reaches vanishing point in at least some cases, and/or (2) that they are a ready means of suicide and as such influence the suicidal rate of the population in an upward direction, and/or (3) that the use of the barbiturates gives rise to addiction.

I am here concerned mainly with the first of these possibilities, namely, that therapeutic doses of the barbiturates are or can be dangerous. In order to examine this question I have had a search made of what I believe to be the entire literature available in this country, with the exception of a few papers, nine in all, of which it has not proved possible to procure copies but to which references had been obtained. (A list of these is appended, and there are in addition a few cases where it has not been possible to procure the original paper, but of which details have been found elsewhere in the literature.) There may be in addition some papers whose existence has not become known to me. A list has been compiled of all the papers reporting fatalities in the literature up to the end of 1932, and each paper has been tabulated according to its year of occurrence, the dose where known, the reasons for its administration, complications where present, the name of the particular preparation, and the author, together with as far as possible the names of the authors who have quoted the same cases elsewhere from time to time. The papers have been subdivided according to the drug used. All fatalities have been tabulated so that as far as possible might be ascertained not only deaths following a therapeutic dose but every other case as well, so as to obtain some idea of the relationship between the ordinary therapeutic dose and the minimum lethal one. The only previous paper on these lines in this country which was read by Young [70], in a discussion in the Therapeutic Section of the Royal Society of Medicine in 1927, stated that up to that date there had been 400 cases of poisoning from the barbiturates recorded in the world literature, of which one-third, or approximately 133, were fatal. A careful check has been made of Young's paper and it has been found that the real number up to that date was 85, the error being produced by counting many cases more than once or even three times. An error of 48 in 85 cases, or 56%, seems somewhat high in a paper referred to by the opener of the discussion at the time, Sir William Willcox [72] as "most carefully compiled," and as one on which he had based some of his views. Since 1927, 44 fatal cases have been recorded in the literature, which brings the total recorded up to the end of 1932 to 157. It is of course true that a number of cases go unrecorded. In this country the machinery of the Coroners' Courts ought to permit of the publication of data in many cases that otherwise become lost to the records, but no official effort is made to ensure this. The use made of Coroners' Courts in this connexion is not scientific.

However, the vast majority of the fatalities are for doses taken with suicidal intent. It is unlikely that fatalities with small doses would escape publication if they were observed at all, except in the most exceptional circumstances of accident or corruption. We may take it therefore that the tables compiled for the purpose of this paper are complete as far as therapeutic doses associated with fatality are concerned.

If we extract from all recorded cases of fatality those in which death occurred from a therapeutic dose we find the following:—

1905 Alter. Veronal gr. 15. Female aged 54. Epileptic.
1913 Willcox. Veronal gr. from 5 to 10. Tabes dorsalis.
1913 Willcox. Veronal gr. 10. No particulars.
1913 Willcox. Veronal and paraldehyde, exact dose not stated. Patient fell 20 feet and had a fractured sternum and ribs.
1915 *Medical Annual*. Veronal gr. 15. No particulars.
1927 Pickworth. Veronal gr. 15, ref. to *Medical Annual* (same case as 1915). No particulars.
1928 Karo. Pernocton 3 c.c. Operation for prostatic disease. Male aged 58.
1929 Eichelter. Pernocton. Operation, resection two-thirds stomach, right side of heart atrophied, excitement before and after ether.

It is obvious that we must rule out for scientific purposes the case referred to by Pickworth and in the *Medical Annual* since nothing but the bare statement is made that death has occurred from a dose of 15 grains. The same fate must overtake Willcox's 1913 "case" with 10 grains of veronal, as he simply says that "cases of death have been recorded even after taking such a small dose as 10 grains." But as he gives few references in his papers on this subject to the work of other authors it is impossible to confirm this statement. They are, nevertheless, apt to be quoted in the foreign literature as "Willcox's cases," without any reference to details other than the alleged doses (e.g. Tardieu [57]). We are left with Willcox's 1913 cases, the first being a man with tabes aged 52, who took a quantity not precisely known, but somewhere between 5 to 20 grains. In this case the author himself at the time said, "in this case it is doubtful if the drug was a factor in producing death," and I believe that most people will agree with him in this opinion.

With regard to the third of Willcox's 1913 cases, he said, "It is extremely doubtful if death was in any way accelerated by veronal." None of these three cases are relevant therefore to the present question.

Alter's case is less simple. This was a woman aged 54, an epileptic who had been ill for some years and had been for a year previous in an institution, and suffered also from repeated dream states. This case of Alter's has been much discussed and opinions both for and against the view that veronal was the main cause of death have been stated. I submit that the following facts are important against this view. The patient was an institutional inmate suffering from epilepsy of undiagnosed origin and there was no autopsy. It seems to me that the probability of its being a barbiturate death is much diminished by the fact that in all the thirty years of experience with veronal since it was introduced there has been no instance of death recorded with doses of this order of magnitude except those which I have mentioned and given reasons for discarding.

In the pernocton cases it appears very dubious to attribute the death solely or mainly to pernocton. Both occurred in elderly persons, after major operations; and in both the death occurred in collapse within a few hours after the operation, a form of death which is quite different from the recognized type of barbiturate death which occurs slowly in coma, after many hours, usually with hypostatic pneumonic signs.

As regards nembutal and Willcox's unqualified statement in the *Practitioner* of

April 1933, that this drug had been responsible in his experience for some deaths, presumably from therapeutic doses, I believe that if three of these cases, constituting the majority of the nembutal cases referred to, were published, the details of which are privately known, it would be quite evident that they did not give unqualified support to the inference that nembutal was dangerous in therapeutic doses. No death from nembutal had in fact been recorded in the scientific literature up to the time of Willcox's statement. Again there is evidence as with most of the barbiturates of a contra-indication in cases of age. A man of 69 had prolonged unconsciousness of thirty-six hours after nembutal but he did not die. The general experience is in fact against the contention of danger in therapeutic doses, at least in people not suffering from some organic disease or the after-effects of a major operation. Curran and Minski at the Maudsley Hospital used doses up to 12½ grains in twenty-four hours sometimes for weeks on end. In collaboration with Dr. Mackintosh and Dr. McNaught the following doses were used for a morphine addict to enable withdrawal of the morphine to be complete, as it was. I can testify that there was never any cause for anxiety.

	July 6	7	8	9	10	11	12	13 to 19	20 to 23
Nembutal grains	24	13½	7½	9	9	8	7½	7½	2½
Chloral grains	50	15	22	25					
Hyoscine grains	1/100th								

Obviously such doses can only be given under the most careful supervision, but the case is of interest in obtaining a balanced view of the question.

As regards repeated doses of the barbiturates the lowest recorded continuous dosage of veronal which was lethal was 174 grains over four days. This represents a considerable excess over the customary daily therapeutic dosage of veronal. Where repeated dosage is too heavy, or if the patient has an idiosyncrasy the fact commonly declares itself in the form of toxic signs which give ample warning: hence doubtless the rarity with which repeated dosage, even if uncontrolled by any attending doctor and in excess of the therapeutic maximum, appears to have proved fatal.

The conclusion of this part of our inquiry is this, that with the barbiturates there is no case on record where either a single dose, or repeated doses, of therapeutic magnitude, has caused death in the absence of complicating factors. No foundation can be discerned on inspection of the facts, for Willcox's statement that "the repeated administration of these barbiturates in one or more daily doses is undoubtedly dangerous."

In complicated cases, i.e. patients with organic disease or after operation there is actually no case on record which would justify attaching the responsibility solely or mainly to a dose of therapeutic magnitude with the possible exception of Alter's.

The words of a continental author, Renner [50] commenting on the comparatively large number of fatalities attributed to veronal in England are very relevant here. He remarks that "what was previously regarded as an 'Act of God' is nowadays attributed to 'poisoning by narcotic drugs,'" and he adds that "it is obvious that the desire to refer things always to precise causes can in practice do violence to exact science."

The margin of safety so far as can be judged from the published records, calculated as the ratio of customary maximum dose to minimum lethal dose is with veronal one in five (taking the maximum dose as 10 grains) and with luminal one in three (taking the maximum dose of luminal as 5 grains). With the newer barbiturates there are not yet enough data to enable the calculation to be made, except by inference from experiments on animals.

The occurrence of idiosyncratic reaction is important: with the barbiturates in general, idiosyncrasy has to be reckoned with in a number of cases. By some authors this is put at 3% but this seems higher than ordinary clinical experience

would suggest. The idiosyncrasy consists either in skin conditions, neurological disturbances, &c., &c. The varieties have been tabulated by Lundy and Osterberg [89]. No case is recorded of a single therapeutic dose, even in an idiosyncratic patient, having a lethal effect.

In continuous doses the only lethal results recorded are those I have mentioned, i.e. only with doses well beyond the therapeutic maximum.

Barbiturates as a means of suicide.—The Registrar-General's statistics for 1931, which are the last complete ones available to me, showed that the total of recorded suicides by all methods was 5,147. Of these the number attributed to the barbiturates was 13, or 0·26%. Even allowing for cases which may have been overlooked, this seems a surprisingly small number, in view especially of the amount of advertisement these preparations have received as a means of suicide by the press.

RELATIVE FREQUENCY OF SUICIDES FROM VARIOUS POISONS. 1931.

1	Lysol	248	
2	Carbolic acid	63	
3	Potassium cyanide	60	
4	Hydrochloric acid	31	
5	Prussic acid	29	
6	Ammonia	28	
7	Oxalic acid	27	
8	Barbituric acid	13	
9	Aspirin	10	
10	Sulphuric acid	7	
11	Strychnine	5	
12	Opium, laudanum, morphia	3	
	Other poisons	106	

SUICIDES BY MEANS OF DRUGS BELONGING TO THE BARBITURIC ACID GROUP. 1931.

Veronal	5
Medinal	2
Somnifaine	1
Dial	1
Allonal	1
Soneryl	1
Aspirin and medinal	1
Adalin	1
Total	13

SUICIDES. 1931.

By solid and liquid poisons and corrosive substances	676
By poisonous gas (all but 12 coal gas)	1,451
By drowning	913
By hanging or strangulation	736
By firearms	267
By cutting or piercing instruments	611
By jumping from high places	167
By crushing	263
By other means	63
Total	5,147

Barbiturates as drugs of addiction.—It is impossible to obtain reliable statistics on this point. Unbiased clinical experience is to the effect that such cases are still rare in this country. In the literature the allegation of addiction sometimes depends on a simple misuse of words. To take a drug in a dose of therapeutic size every night for, say, four months for the purpose of relieving insomnia is not addiction if the word is to have any meaning. A number of the cases recorded in the literature as addiction are only so classed as the result of this looseness of terminology.

FATALITIES FROM THE BARBITURIC ACID GROUP OF DRUGS

Ref No.	Year	New cases	Fatalities	Dose gr.	Dose gm.	Suicide, Therapeutic, Accident or Addiction	Drug	Complications	Old cases	Old Fatalities
1	1905	1	1	7½, 15, 30 daily for 11 months	0·5, 1, 2	Add.	Veronal	—	—	—
2	,,	1	1	15	1	Th.	,,	Epilepsy	—	—
3	,,	1	1	150	10	Acc.	,,	—	—	—
4	,,	1	1	?	—	? S.	,,	—	—	—
5	,,	1	1	23-46	—	—	,,	Cardiac weakness and severe operation	—	—
6	,,	1	1	—	—	—	,,	—	—	—
7	,,	—	—	—	—	—	,,	—	1	1
8	,,	1	1	250	—	S.	,,	—	—	—
9	1906	2	2	463	—	S.	,,	—	—	—
,,	,,	—	—	170	—	S.	,,	—	—	—
10	,,	1	1	310	—	S.	,,	—	4	4
11	,,	2	2	123-154	—	S.	,,	—	—	—
,,	,,	—	—	93	—	S.	,,	—	—	—
12	,,	1	1	154	—	? S.	,,	Alcoholic ? and ? tabes ...	—	—
13	1907	—	—	—	—	—	,,	—	7	7
14	,,	1	1	?	—	—	,,	—	—	—
15	,,	1	1	170	—	S.	,,	—	—	—
16	1908	1	1	60	—	—	,,	Confinement. Child also died	—	—
17	,,	1	1	139 in 3 dys.	—	—	,,	—	—	—
18	,,	1	1	150	—	S.	,,	—	—	—
19	,,	10	10	—	—	—	,,	—	—	—
20	1909	1	1	About 100	—	S.	,,	—	—	—
21	,,	1	1	?	—	S.	,,	—	—	—
22	,,	2	2	?	—	? S. ? Add.	,,	—	—	—
,,	,,	—	—	?	—	? S. ? Add.	,,	—	—	—
23	,,	—	—	—	—	—	,,	—	12	12
24	,,	1	1	91	—	? S.	,,	—	—	—
25	1911	1	1	—	—	—	,,	—	—	—
26	,,	1	1	—	—	—	,,	—	—	—
27	1912	1	1	?	—	S.	,,	—	—	—
28	,,	1	1	85	5·40	—	,,	—	—	—
29	,,	2	2	—	25	S.	,,	—	—	—
,,	,,	—	—	—	10	S.	,,	—	—	—
30	,,	—	—	—	—	—	,,	—	2	2
31	,,	2	2	252 in 5 days 177	—	Add. S.	,,	Alcoholic	—	—
32	,,	2	2	115	—	S.	,,	—	—	—
33	,,	—	—	189	—	S.	,,	—	—	—
34	1913	2	2	139	9	S.	,,	—	2	2
35	,,	—	—	154½	10	S.	,,	—	—	—
36	1913	1	1	150	—	S.	,,	—	—	—
37	,,	8	8	?	—	? S.	,,	Œdema and static congestion of lungs	—	—
,,	,,	—	—	?	—	? Add.	,,	Malignant growth in stomach, scirrhous growth left breast	—	—
,,	,,	—	—	? 5	—	—	,,	Tabes dorsalis	—	—
,,	,,	—	—	?	—	? Add.	,,	Pneumonia and heart failure	—	—
,,	,,	—	—	?	—	? Add.	,,	—	—	—
,,	,,	—	—	?	—	Th.	,,	Fell 20 ft., fractured sternum and ribs	—	—
,,	,,	—	—	? 100	—	S.	,,	—	—	—
,,	,,	—	—	? 150	—	S.	,,	—	—	—
38	1914	1	1	120	—	Acc.	,,	—	—	—
39	,,	3	3	—	—	—	,,	—	—	—
40	,,	1	1	90	—	—	,,	—	6	6
41	,,	1	1	15-50	—	? S.	,,	—	—	—

RECORDED IN THE LITERATURE TO THE END OF 1932.

Author	Reference	Quoted in Literature by	Remarks
Kress	*Therap. Monat.*, 1905, xix, 470 ...	Givkovitch-Radomir, A. Tardieu, Caussade and Lejard, Hamilton, Geiger and Roth, Schneller, Lebeaupin, Bosquet	—
Alter	*Münch. med. Woch.*, lii, 514 ...	Jacobi, Vallon and Bessière, Tardieu, Lebeaupin, Bosquet, Steindorff	Doubtful
Harnack ...	*Münch. med. Woch.*, 1905, lii, 2269	Jacobi, Huseman, Tardieu, Nienbaus, Umber	Holzenminder case
Farncomb ...	*Can. Pract. and Rev.*, xxx, 681 ...	Lundy and Osterberg	—
Friedal	*Zeits f. med.-Beamte.*, 1905, xvi, 770	Jacobi, Boenheim, Huseman, Umber	—
Lewinski ...	*Zahnartzl. Rundschau.* Berl., 1905, xiv, 837	—	Original not seen
Anon.	*Boston M. and Surg. J.*, cliv, 113	—	—
Germann ..	*J.A.M.A.*, xlvi, 1999	Boston, M. J.	—
Ehrlich	*Münch. med. Woch.*, 1906, xii, 599	Vallon and Bessière, G.-Radomir, Jacobi, Boenheim, Nienhaus, Umber	—
,,	—	Jacobi, Boenheim, Pollitzer, Nienhaus, Umber, Steindorff	Parisers case
Umber	*Med. Klin.*, 1906, ii, 1254, and *Münch. med. Woch.*, 1906, liii, 2556	Steindorff, Schubiger, Tardieu, Boenheim	—
Zornlaib ...	*Wien. med. Woch.*, 1906, lvi, 2454	— Jacobi, Boenheim, Huseman	— —
,,	—	—	—
Hampke ...	*Inaug. Diss.*, Leipzig, 1906 ...	Jacobi, Huseman	Young quotes as ?
Nienhaus ...	*Cor. Bl. f. Schweiz. Aerzte*, Basel, 37-336	Schubiger	—
Gwozdecki ...	*Lwow Ygon. leh.*, 1907, ii, 221	—	Not seen
Schneider ...	*Prager med. Woch.*, 1906, 435 ...	Jacobi, Boenheim, Nienhaus	Original not seen
Parsons ...	*B.M.J.*, 1908 (ii), 832	—	—
Koch	*Nederland Tijdschr. v. Gen.*, Amst. 2 R., xliv, 1 Afd., 326 ...	Huseman (in full)	Not seen
Stucky	*Louisville Monthly. Journ. Med. and Surg.*, xiv, 241	Lundy and Osterberg	Not seen
Panzer	*Vrtljschr. f. ger. Med.*, xxxii, 311	—	P.M. material only. No clinical records
Davies	*B.M.J.*, 1909 (ii), 1154	Munro, Macrae and College	—
Anon.	*B.M.J.*, 1909 (ii), 1321	—	—
,,	*Lancet*, 1909 (ii), 760	—	—
,,	,, ,, ,,	—	—
Jacobi	*Vrtljschr. f. ger. Med.*, Berlin, xxxvii, 222	Schubiger, Steindorff	—
Walker	*Lancet*, 1909 (i), 1557	—	—
Heiduschka ...	*Arch. de Pharm.*, Berlin, ccxlix, 322; *Chem. Abstr.*, 1911, v, 3288	Lundy and Osterberg	Not seen
Veress	*Budapesti Orw. Ursag.*, ix, 226	—	Not seen
Anon.	*Pharm. Journ.*, Lond., 1910	—	—
McLean... ...	*Lancet*, 1912 (i), 647	Tardieu	—
Romell	*Charité Ann.*, Berlin, xxxvi, 62	—	—
	—	—	—
Pollitzer ...	*Journ. Cutan. Dis.*, N. Y., xxx, 185	Lundy and Osterberg	—
McCrae and College	*Pharm. Journ.*, London, 4th series, xxxiv, 724	—	—
Weitz	*Festschr. f. d. alleg. Krankenhaus. St. Georg.*, 1912	Boenheim	—
,,	,,	,,	—
Vallon and Bessière	*L'éncephale*, Paris, 1913, viii, 233	—	First rep. by Bahrlet, ref. not known
Editorial" ...	*B.M.J.*, 1913 (i), 566	—	—
Willcox	*Lancet*, 1913 (ii), 1178	—	—
,,	,,	—	—
,,	,,	Tardieu	Tardieu quotes without mentioning complications
,,	,,	—	—
,,	,,	Tardieu	—
,,	,,	—	—
,,	,,	—	—
Fraser	*Lancet*, 1914 (i), 1736	Munro	—
Jansch	*Forensic Med.* (Alex. Kolisko ed.) ii	—	Not seen
Munro	*B.M.J.*, 1914 (i), 854	Schubiger	No ref., no details
Russell and Parker	*B.M.J.*, 1914 (i), 853	,,	—

Ref. No.	Year	New cases	Fatalities	Dose gr.	Dose gm.	Suicide, Therapeutic, Accident or Addiction	Drug	Complications	Old cases	Fatalities
42	1915	1	1	?	—	? Add.	Veronal	—	12	12
43	1917	1	1	—	15 grm. in 8 days	Add.	,,	—	5	5
44	1918	2	2	?	—	?	,,	—	—	—
45	,,	2	2	?	—	? Add.	,,	—	—	—
,,	,,	—	—	46/61	3-4	—	,,	Alcoholic	—	—
46	,,	1	1	75	—	S.	,,	—	—	—
47	,,	1	1	—	5-6	—	,,	—	—	—
48	1919	2	2	?	—	? S.	,,	Positive Wassermann ...	—	—
,,	,,	—	—	?	—	? S.	,,	Veronal and morphia found in urine	—	...
49	1922	5	5	155	10	S.	,,	Previous non-fatal attempt with 155 gr.	17	17
,,	,,	—	—	185	12	S.	,,	—	—	—
,,	,,	—	—	232	15	S.	,,	—	—	—
,,	,,	—	—	?	?	S.	,,	—	—	—
,,	,,	—	—	?	?	S.	,,	—	—	—
50	1922	—	—	—	—	—	,,	—	? 26	? 26
51	,,	1	1	—	—	—	,,	—	—	—
52	1923	1	1	—	4-5	S.	,,	—	—	—
53	,,	1	1	—	5	? S.	,,	—	—	—
54	,,	1	1	—	4-5	—	,,	—	—	—
55	,,	1	1	300 in 4 wks. 174 in 4 dys.	—	—	,,	—	—	—
56	,,	1	1	—	5	—	,,	Psychopathic but organically sound	—	—
57	1924	1	1	A week's supply	—	—	,,	—	13	13
58	,,	—	—	—	—	—	,,	—	1	1
59	,,	—	—	—	—	—	,,	—	2	2
60	,,	2	2	?	?	S.	,,	—	—	—
,,	,,	—	—	?	?	S.	,,	—	—	—
61	,,	1	1	—	12	—	,,	—	7*	7
62	1925	Several		—	—	—	,,	—	—	—
63	,,	1	1	—	? 10	S.	,,	—	—	—
,,	,,	1	1	—	?	S.	,,	—	—	—
,,	,,	1	1	—	?	S.	,,	—	—	—
64	,,	—	—	—	—	—	,,	—	4	4
65	,,	—	—	—	—	—	,,	—	1	1
66	,,	1	1	—	15	S.	,,	—	1	1
67	,,	—	—	—	—	—	,,	—	1	1
68	,,	11	11	—	?	S.	,,	—	—	—
69	,,	—	—	—	—	—	,,	—	?	1
70	1927	1	1	50-100	—	—	,,	—	—	—
71	,,	—	—	—	—	—	,,	—	1	1
72	,,	19	19	?	—	Add.	,,	—	—	—
,,	,,	—	—	? 150	—	? S.	,,	—	—	—
,,	,,	—	—	? 100	—	S. & Add.	,,	—	—	—
,,	,,	—	—	large dose	—	S. & Add.	,,	—	—	—
,,	,,	—	—	,,	—	S.	,,	—	—	—
,,	,,	—	—	?	—	? S.	,,	—	—	—
73	,,	1	1	150	10	S.	,,	—	—	—

Fatalities	Author	Reference	Quoted in Literature by	Remarks
12	Huseman ...	*Vrtljschr. f. ger. Med.*, 1915, xlix, 150	—	Final dose unknown. Addiction alleged
5	Schubiger ...	*Cor. Bl. f. Schweiz. Aertz.*, Basel, xlvi, 1741	—	—
—	Editorial ..	*B.M.J.*, 1918 (i), 182	—	Doses not given
—	Weitz	*Med. Klin.*, 1918, xiv, 159	—	—
—	,,	,,	—	—
—	Gautier	*Rev. méd. de la Suisse Rom.*, Geneva, xxxviii, 641	—	—
—	Roy des Barres ...	*Bull. de la Soc. méd. chirg. de l'Indo-Chin.* (*déc.*) 1918	Tardieu, Givkovitch-Radomir ...	—
—	Römer	*Deutsche. med. Woch.*, 1919, xlv, 1305	—	Dose unknown. Men found unconscious
...	,,	,,	—	—
17	Boenheim ...	*Med. Klin.*, 1921, xvii, 1263	—	—
—	,,	,,	—	—
—	,,	,,	—	—
—	,,	,,	—	—
—	,,	,,	—	—
? 26	Renner	*Zeit. f. Aertzl., Fortbildung*, xix, 327	Bofinger	
—	Belorhadsky ...	*Z'bt. f. inn. Med.*, 12, 1416 ...	Boenheim	Ref. given by Boenheim. ? Cannot trace original
—	Herz	*Deutsch. med. Woch.*, xlix, 416 ...	Tardieu	—
—	Bofinger ...	*Ibid.*, xlviii, 1518	Herz	—
—	Ortner	*Wien. med. Woch.*, lxxiii, 631	—	—
—	Cole	*J.A.M.A.*, lxxx, 373	Lundy and Osterberg	—
—	Kromer	*Zeit. f. Aerztl. Fortbildung*, Jena, xx. 461	Lundy and Osterburg	—
13	Tardieu	*Thèse de Paris*, 1924, 511	—	—
1	Tardieu and Medioni	*Journ. de Méd. de Paris*, xlii, 354	Achard	—
2	Tardieu	*Rév. de Méd.*, 7, xli, 393.	—	—
—	Ipsen	*Wien. med. Woch.*, lxxiv, 2025	—	—
—	,, ...	,, ,,	—	—
7	Givkovitch-Radomir	*Thèse de Paris*, 1924, 411	—	—
—	Leake and Ware...	*J.A.M.A.*, lxxxiv, 434	—	No details of individual cases
—	Rivet, Jany, and Herbain	*Bull. et mém. Soc. Méd. d'Hóp de Paris*, 1925, xlix, 276	Achard	—
—	Huber			
—	Massary			
4	Steindorff ...	*Deutsch. med. Woch.*, li, 1565	—	*See* 97
1	Caussade, Tardieu and Lejard	*Bull. et mém. Soc. Méd. d'Hóp de Paris*, xlix, 1483	—	—
1	Sidney Smith ...	*Forensic Medicine*, 373	—	Death occurred in less than 12 hours
1	Paris Correspondent	*J.A.M.A.*, lxxxiv, 1134	—	—
—	Redlich ...	*Wien. med. Woch.*, 1926, lxxvi, 139	—	No clinical details
1	Levent	*Gaz. d'hôp. de Paris*, xcix, 479	—	—
—	Young	*Proc. Roy. Soc. Med.*, 1927, xx, 1498	—	Young quotes another case as fatal, but there is no direct evidence that the patient ever took a barbiturate
1	Pickworth ...	*Ibid.*, 1927, xx, 1486	—	—
—	Willcox	*Ibid.*, 1927, xx, 1480	—	—
—	,, ...	—	—	—
—	,, ...	—	—	—
—	,, ...	—	—	—
—	,, ...	—	—	—
—	,, ...	—	—	—
—	Dumitresco-Mante	*Bull. et mém. Soc. Méd. d'Hóp de Bucharest*, 1927, ix, 912	Lundy and Osterberg	In 13 other cases only p.-m. findings and no clinical details are given
				Not seen

Ref. No.	Year	New cases	Fatalities	Dose gr.	Dose gm.	Suicide, Therapeutic, Accident or Addiction	Drug	Complications	Old cases	Fatalities
74	1928	1	1	—	5*	S.	Veronal	—	—	—
75	,,	?	1	? 200	—	—	,,	—	—	—
76	1929	—	—	—	—	—	,,	—	3	3
77	,,	1	1	—	10	S.	,,	—	—	—
78	1932	1	1	—	4·602	S.	,,	—	—	—
79	,,	—	—	—	—	—	,,	—	—	—
80	,,	2	2	—	—	—	,,	—	—	—
81	,,	1	1	—	?	S.	,,	—	—	—
82	1913	1	1	125	—	S.	Medinal	—	—	—
83	1926	1	1	?	—	Add.	,,	—	—	—
84	1927	3	3	200	—	S.	,,	—	—	—
,,	,,	—	—	?	—	?	,,	—	—	—
,,	,,	—	—	?	—	?	,,	—	—	—
85	1932	—	—	—	—	—	,,	—	—	—
86	,,	1	1	—	100 tablets	S.	Allonal	—	—	—
87	1928	1	1	3 c.c.	—	Th.	Pernocton	Aged 68, prostatic disease	—	—
88	1929	1	1	0·02 grm. morphine 0·001 grm. atropine 0·0071 pernocton per kilo body-wt.		Th.	Morphine atropine pernocton	Gastric ulcer	—	—
89	,,	—	—	—	—	—	Luminal	—	2	2
90	1919	1	1	40 and 10 c.c. tinct. opii	—	S.	Luminal and opium	Psychopathic	—	—
91	,,	1	1	—	15 in 28 days	Th.	Luminal	Tb. and epilepsy	—	—
92	1920	3	3	?	?	?	,,	—	—	—
,,	,,	—	—	—	2 in 24 hrs.	—	,,	—	—	—
,,	,,	—	—	—	3·4 in 6 hrs.	—	,,	—	—	—
57	1921	1	1	?	?	—	,,	—	—	—
94	1924	—	—	—	—	—	,,	—	1	1
95	1925	1	1	15	1	—	,,	Woman 67, arteriosclerosis ...	—	—
96	1926	—	—	—	—	—	,,	—	1	1
97	1925	1	1	?	?	Add.	Luminal, veronal, adelin, pontopon	—	—	—
98	1926	—	—	—	—	—	Luminal	—	5	5
84	1927	1	1	?	?	?	,,	—	—	—
99	1929	1	1	?	?	Add.	,,	—	—	—
100	,,	1	1	—	12	S.	,,	—	8	8
89	,,	—	—	—	—	—	,,	—	2	2
101	1932	3	3	—	2·3	S.	,,	Epilepsy	—	—
,,	,,	—	—	—	?	S.	,,	,,	—	—
,,	,,	—	—	—	?	S.	,,	,,	—	—
102	,,	1	1	—	3·4	S.	,,	,,	—	—
103	,,	2	2	—	0·5 daily 1 yr.	Th.	Sevenal	,,	—	—
,,	,,	—	—	?	?	S.	,,	—	—	—
94	1924	1	1	—	?	? S.	Dial	—	—	—
105	1925	2	2	—	0·80 and 4 tab. veronal	S.	Dial and veronal	—	—	—
,,	,,	—	—	—	2	S.	Dial	—	—	—
106	1929	1	1	—	1·9	S.	,,	—	—	—
58	1924	1	1	—	30 drops and 6 c.c.	—	Somnifene	Laennec's cirrhosis	—	—
57	,,	—	—	—	—	—	,,	—	1	1
107	1925	1	1	—	10 c.c. intramuscular	Th.	,,	Attempted suicide by jumping out of window	—	—
108	,,	1	1	—	10 c.c. intravenous	Th.	,,	—	—	—
109	1928	1	1	—	13 c.c.	S.	,,	—	—	—
110	1929	—	—	?	—	—	,,	—	—	—
89	,,	—	—	—	—	—	,,	—	2	2

Author	Reference	Quoted in Literature by	Remarks
Paolini	*Riforma. med.*, 1928, xliv, 1069 ...	—	At least 5 grm., probably double
Work	*Arch. of Neurol. and Psychiat.*, 1928, xix, 327	Lundy and Osterberg	—
Achard	*Journ de méd. et chirg. pract.*, c, 279	—	—
Schröder ...	*Deutsch. Zeit. f. ges. ger. Med.*, 1929, xiii, 353	—	—
Grönover ...	*Samml. f. Vergiftungsfällen*, 1932, iii, 145	—	—
Laborde and Duquénois	*Journ. de pharm. et chim.*, xvi, 479	—	Not seen
Trevisanello ...	*Gazz. internal. med. chir.*, xl, 458	—	Not seen
Petri, Else ...	*Virchow's Arch. f. path. anat.*, 1932, cclxxxiv, 84	—	—
Willcox ...	*Lancet*, 1913 (ii), 1178	—	—
Stolkind ...	*Lancet*, 1926 (i), 391, and *Proc. Roy. Soc. Med.*, xx, 1506	—	—
Willcox ..	*Proc. Roy. Soc. Med.*, 1927, xx, 1503	—	—
,, ...	,, ,,	—	—
,, ...	,, ,,	—	—
Incze	*Orvosi hetil*, 1930, lxxiv, 830	—	Not seen
Balázs, J. ...	*Samml. v. Vergiftungsfällen*, 1932, iii, 139	—	Dosage of tablets not stated
Karo	*Munch. med. Woch.*, 1928, ii, 1555	Lundy and Osterberg	—
Eichelter ...	*Zentralb. f. Chirg.*, lvi, 2378 ...	,, ,,	—
Lundy and Osterberg	*Proc. Mayo Clinic*, 1929, iv. 386	—	—
Rosenberg ...	*Med. Klin.*, xv, 1150	—	—
Heuber	*Munch. med. Woch.*, 1919, lxvi, 1090	G.-Radomir, Schneller, Hamilton, Geiger and Roth	30 doses
Nolte	*Pharm. Zeit.*, 1920, 320	Schneller	Orig. n/s } Luminal not found P.M.
,, ...	,, ,, ,, ,,	,,	,, }
,, ...	,, ,, ,, ,,	,,	,, }
Tardieu ..	*Thèse de Paris*, 1924, 511 ...	—	Chavigney and Rullman's case
Givkovitch, Radomir	*Thèse de Paris*, 1924, 411 ...	—	—
Weig	*Deutsch. med. Woch.*, 1925, li, 272	Lundy and Osterberg	—
Hamilton, Geiger and Roth ...	*Illinois Med. Journ.*, xlix, 344	—	—
Steindorff ...	*Deutsch. med. Woch.*, li, 1565 ...	—	—
Schneller ...	*Deutsch. Zeit. f. ges. ger. Med.*, 1928, vii, 265	—	—
Willcox	*Proc. Roy. Soc. Med.*, xx, 1303 ...	—	P.-M. analysis only, no clinical details
Wright, N. ...	*Arch. Inter. Med.*, xliii, 85 ...	Lundy and Osterberg	—
Achard	*Journ. de Méd. et chir. pract.*, c, 279	—	—
Lundy and Osterberg	*Proc. Mayo Clinic*, 1929, iv, p. 386	—	—
Schou, A. H. ...	*Ugesk. f. Laeger*, cxiv, 492	—	—
—	,, ,,	—	—
—	,, ,,	—	—
Clemenson ...	*Ugesk. f. Laeger*, cxiv, 493	—	—
Jankovitch and Fazekas ...	*Monat. f. Psychiat. u. Neurol.*, lxxxiv, 15	—	—
,, ...	,, ,, ,, ,,	—	—
Givkovitch, Radomir	*Thèse de Paris*, 1924, 411	—	—
Achard, Mouzon and Bloch ...	*Bull. de l'Acad. de Med.*, xciii, 732	—	—
—	—	—	—
Van Itallie and Steenhauer ...	*Samml. v. Vergiftungsfällen*, 1932, iii, 141	—	—
Tardieu and Medioni	*Journ. de Méd. de Paris*, xliii, 354	Lundy and Osterberg	—
Tardieu... ...	*Thèse de Paris*, 511	—	—
Caussade, Tardieu and Lejard ...	*Bull. et mém. Soc. Méd. d'Hôp. de Paris*, 1925, xlix, 1483	Ravina and Girot	Quercy and Lancelot's case
Ravina and Girot	*Bull. et mém. Soc. Méd. d'Hôp. de Paris*, 1925, xlix, 370	Achard	—
Hammer ...	*Deutsch. med. Woch.*, liv, 1340	Lundy and Osterberg	—
Milewski ...	*Polska. gaz. lek.*, viii, 107	—	Not seen
Lundy and Osterberg	*Proc. Mayo Clinic*, 1929, iv, 386 ...	—	—

Dr. G. W. B. James said he thought it would be interesting to consider the attitude of practitioners themselves towards the question of prescribing hypnotic drugs. That attitude, in his view, could be conveniently divided into three stages.

The first stage was brief, and perhaps most of the members present could recall the anxiety experienced by young physicians after the first full doses of ordinary hypnotics had been prescribed. Every moment after the prescription was dispensed was spent in apprehensive expectation, and it was with difficulty that the prescribers restrained themselves from making frequent calls to ascertain whether the patient was still breathing. After a short time this apprehensive stage was followed by a second stage which lasted longer. In this the practitioner lost his early fears, and in some instances entered upon a somewhat indiscriminate use of hypnotics—the kind of prescribing which was one of the chief dangers of the use of these drugs. In this the doctor was encouraged by a public demand, and by a proper anxiety not to be regarded by patients as ill-informed or out of date. The medical man was also stimulated by a constant flow of free samples and desk blotters from the manufacturers. The folder enclosed in the samples assures him the newest drug produced no unpleasant results, was quickly eliminated and produced natural and refreshing sleep without subsequent depression. During this second stage doctors' doses tended to increase, there was a determination to try every new preparation. This stage lasted a variable time, its duration might be determined by an accident, or, more happily, the critical attention and interest of the doctor was roused by some alarming idiosyncrasy.

He could himself claim to have passed through those two stages, and it might interest those present to hear of an incident which had impressed him in his early prescribing career when he was taking charge of a patient who was the subject of severe alcoholism: he was, in fact, the only man he (the speaker) had ever known who drank his whisky-and-soda from the wash-basin. He (Dr. James) and his patient had rooms in the same hotel, and, in the usual suspicious mood the patient insisted that he (Dr. James) should share the treatment. It was the only way in which the man could be induced to take what was ordered for him. On the first night, therefore, each swallowed a 15 grain cachet of medinal. That gave the patient some six hours of sleep, but he (Dr. James) had to be forcibly turned out of bed in the morning by the attendant, who, naturally, thought that he had been drinking, and almost wrote to the responsible relatives. On the next and succeeding nights his (the speaker's) cachet contained sugar of milk only, but it was several days before he lost the unpleasant diplopia which followed the first taking of the drug.

He apologized for reciting this experience because it merely called attention to a personal idiosyncrasy, familiar enough in practice. But it was the experience which introduced him to the third stage of the practitioner's attitude towards hypnotics, the stage which endured to the end of professional life. It was marked by adherence to a comparatively short list of well-tried hypnotics with which the doctor was thoroughly familiar. It was also marked by a much greater attention to the innumerable factors which made up the problems of insomnia or psychomotor restlessness, neither of which could be adequately treated by chemical substances alone. He was anxious not to give the impression, from his remarks, that he considered medinal dangerous; he used it personally, and he regarded it as a valuable hypnotic, and he had only met one case of medinal addiction. He wished, rather, to stress the necessity for vigilance in using hypnotics, and to enter a plea for the employment of smaller doses than those commonly given. There were, of course, exceptions: many patients met with in psychiatric practice required large doses. For the alcoholic friend of whom he had spoken, he would now prescribe 5 or 6 drachms of paraldehyde.

He would like to refer to the bromides. In examining the pharmacopœias of several teaching hospitals one would find stock mixtures containing 15 grains of

bromide to be given thrice daily. To many patients the giving of such a dose was undesirable. For example, one could take the case of a woman who had puerperal sepsis and a tendency to mental confusion. Doses of the strength he had named would cause an increase in the patient's confusion, and a tendency to the production of hallucinations, or illusions of sight, and still would fail to procure for the patient the desired sleep. The findings of Notkin, Killian, and other writers on the blood changes produced by bromide therapy confirmed him (Dr. James) in his dislike of bromides.

There was so much that was personal in the use of hypnotics that it was impossible to lay down precise rules for their sale or prescription. Until the action of hypnotics was placed on a scientific basis it might be difficult to introduce useful legislation; it was especially undesirable for legislation to suggest that the public required to be protected from dangerous drugs as used by physicians. He considered that in practice hypnotics were often withheld too long. It was important not to let a patient acquire what Sir William Willcox referred to as the "obsession of insomnia." The main danger lay in indiscriminate experimental prescribing, as he had often observed.

Professor Alfred Meyer: The work done up to the present on the anatomical changes in the brain, produced by hypnotics, gives no unequivocal answer to the question of their pathogenesis. However interesting some of them are, they do not permit general conclusions. Some authors, as for instance Weimann, Petri, Yankovich and Fazekas, have described changes which may point to a damage of blood-vessels or a lack of blood supply. The peculiar mucinoid bodies in the experimental cases of Mott, Woodhouse, and Pickworth, and the metachromatic ones described recently by van der Horst and Hasselt still lack an explanation. Many authors are influenced by the idea that the toxic effect of hypnotics is an increased therapeutic one, showing itself in primary ganglion cell degenerations at the place where the drug is expected to attack. The difficulty is that ganglion-cell degeneration may be due to accidental ante- or post-mortem, or even technical, conditions. Especially in the brain-stem misinterpretation is frequent, as recently shown by Bodechtel and Gagel. The more we gain experience, the more reserved we become. Of course, I do not deny the possibility of direct toxic action on ganglion cells in any case, but very often the pathogenic course is different. For instance, Spielmeyer and his pupils have drawn attention to the importance of functional vascular troubles. We possess an instructive example in our experimental results, obtained by poisoning with narcotics, cyanide of potassium and carbon monoxide. (The narcotic experiments have been carried out together with Dr. Blume, pharmacologist in Bonn.) The slides which I want to demonstrate to you prove that carbon monoxide, cyanide of potassium, and narcotics, however much their chemical structure and specific action may differ, lead to brain changes identical both as to quality of the process and distribution. We could detect ischæmic necroses and softenings in cortex, white matter, corpus callosum, globus pallidus, red zone of substantia nigra and the sector of Sommer of the cornu ammonis. We must add that these may also occur after morphine intoxication (Weimann and Mahrenholtz) and asphyxia of other origin (Rotter). It is the anoxæmia—according to Quastel, in a sense which includes not only the lack of oxygen but also the condition rendering the oxygen unavailable for oxidative purposes—which acts as the common pathogenic factor and which determines the distribution of the process. Even the selective lesion of the globus pallidus, formerly regarded as a specific response to carbon monoxide, becomes only a by no means rare expression of vulnerability against asphyxia. Whether we have to expect similar occurrences with some of the hypnotics is still an open question. The above-mentioned views of Quastel make it to a certain extent probable. The somnifene case of van der Horst and Hasselt

shows that respiratory failure can occur. I once found, after veronal poisoning, an unusual amount of pseudo-calcium in the globus pallidus as perhaps the first step towards lesion. In this respect the clinical observation, by Mussio-Fournier, of a Parkinson syndrome after veronal addiction may be remarkable. It will be the task of further experimental work to clear up these questions, and I hope that my previous experiments may constitute a valuable model.

Dr. Desmond Curran: With the encouragement and advice of Dr. Mapother, Dr. Louis Minski and myself conducted an investigation on the value of nembutal for the patients we had under us at the Maudsley Hospital.

For the purposes of this communication the results obtained during a period, from January 1932, when we started, until March of this year, will be given very briefly.

During this period of some fourteen months, 24,000 grains of nembutal were dispensed and 328 patients received it.

These patients differed widely in the type and degree of severity of their illness, ranging from mild anxiety states to acute mania. They can probably be considered to be a representative sample of the cases met with in psychiatric practice for whom nembutal is likely to be prescribed. We had, however, from the nature of the hospital, relatively little opportunity for trying the effects of the drug on cases suffering from the more chronic and irrecoverable forms of mental disorder, such as senile and arteriosclerotic dementia and the schizophrenias of long standing.

At first nembutal was given alone to the exclusion of all other drugs. As might have been expected from its rapid and relatively transient action, it soon became apparent that in the dosage we employed (and we never gave more than 13½ grains in the twenty-four hours), its value as a continuous sedative in cases of prolonged excitement or agitation was limited, though it proved of considerable value in cases which exhibited episodic or periodic outbursts of agitation or restlessness. From the first we found it a hypnotic of very great value, and we also found it to be of great service in the performance of the minor operations that came our way, such as the taking of blood or lumbar puncture in apprehensive and sometimes actively resistive subjects.

As regards administration, it was essential to give the drug in a concentrated solution and on an empty stomach. It soon became our practice to begin with 3 grains as a hypnotic and to increase this by 1½ grains until the desired effect was produced. We have never given more than 6 grains as a single dose, and 4½ grains has usually sufficed. For sedative purposes and minor operations our dosage was similar. It became our strict rule not to begin with more than 3 grains as the initial dose, should the general physical condition be very poor, and naturally children received smaller quantities.

The action was usually apparent in half an hour. The period of most profound action was short-lived, in the day usually another half hour. After this the patients usually passed into a condition of light sleep or drowsiness. The total duration of effect varied considerably and was strikingly dependent upon stimuli in the external environment, the patients being readily awakened by outside noise or disturbance. For this reason much better effects were obtained when side rooms could be employed. On the whole it seems fair to say that an average dose of 4½ grains in the day time was roughly as effective, but not so certain in its action, as 2 drachms of paraldehyde. It had the great advantage of being much more palatable.

As has been indicated we soon formed and have retained a very high opinion of nembutal as a hypnotic. It appeared to be of particular value in the not infrequent cases who experience a difficulty in going off to sleep, and whose increasing anxiety and tension as the hours pass is not conducive to the effect they so much desire. Such patients have often the next day expressed their relief that their fears of yet

another sleepless night had been so rapidly terminated. We are not convinced that we have seen a case in which a true tolerance has been developed. In many cases we have given it continuously for weeks, and with as good effects at the end as the the beginning. There has been, however, considerable individual variation in susceptibility to the drug.

On only two occasions have we seen any effects that were at all alarming. Two patients, both emaciated and in a very poor state of general health, one of them in addition being alcoholic, collapsed, and became pulseless with 4½ grains. Both were quite well later on the same day. These two patients were amongst the first to whom we gave the drug, and were indeed the occasion for our subsequent rule that not more than 3 grains should be given as an initial dose to the physically debilitated. We have never on any subsequent occasion had any experience to cause us alarm or even anxiety.

As regards other untoward effects, a few patients have complained of nausea, fewer still have actually vomited. An occasional patient has complained of giddiness. On the whole the freedom from any unpleasant after-effects has been very striking, and in our experience fewer patients complain of heaviness the next morning than after medinal.

We have given nembutal to patients who were also receiving medinal, bromide, chloral, hyoscine, paraldehyde and somnifaine. We have never thereby experienced cause for uneasiness. It may be of interest to give some of the larger doses in combination we have given in twenty-four hours:—

Nembutal gr.	13½	with hyoscine gr.	1/30
,, ,,	10½	,, paraldehyde	℥ij
,, ,,	9	,, medinal gr.	x
,, ,,	9	,, paraldehyde	℥ij
,, ,,	7½	,, paraldehyde	℥iv
,, ,,	6	,, br. gr.	30
,, ,,	4½	,, br. gr.	60, chloral gr. 45 (this was continued for some weeks), occasionally also paraldehyde ℥ij

By far the largest single dose that has come to our knowledge was in the case of a man who the night before an operation in another hospital, was given nembutal in preparation for N. anæsthesia the next morning. He received 15 grains owing to an error. We were told he became violently excited and then somewhat collapsed, had his stomach washed out and passed into sleep. He sustained a very severe operation the next day with complete success, for which only a light additional anæsthetic proved necessary.

As the result of an increasing experience, we have seen no reason to modify the conclusions we have given elsewhere. These were that nembutal in 3 to 6 grains is a hypnotic of the greatest value, not unpleasant to take, reasonably certain in its action, devoid of risk, and free from unpleasant after-effects. In similar doses it provides a sedative of value in cases with episodic or periodic outbursts of agitation and restlessness. It is also of great service in minor surgical operations, both to facilitate their performance and to avoid the fear and anxiety especially in children, which might otherwise have been caused. In our experience it can be safely combined with large doses of other drugs. It would seem a pity if advantage should not be taken of such a useful addition to the pharmacopœia through a reputation for danger, which if reasonable precautions are taken, it does not appear to deserve.

Sir Maurice Craig said that his object in attending the meeting was to learn, and he had learned a good deal. For years he could not understand how two practising physicians, such as Sir William Willcox and himself, had come to such widely opposite views on the barbituric acid group. The riddle had been solved this

evening when Sir William told the meeting that he had never prescribed any of these drugs. That statement meant that he had no clinical experience in the therapeutic use of these hypnotics. Therefore his observation on the clinical values of them could be of little or no use, as he had never observed their action on his own patients. Sir William Willcox spoke as a distinguished toxicologist, and as one who had seen bad effects or even disasters, but the history leading up to these would embrace other matters than purely therapeutic experience.

The second point that he (the speaker) wished to make was the unscientific way in which a few cases were constantly being quoted in support of the dangerous effect of these drugs. What weight did these carry in comparison with the many thousands of times these drugs were prescribed by medical men?

There was also the astounding statement that Sir William Willcox made that those who took sedatives for prolonged periods commonly ended in taking their lives. If this were true the papers and the coroners' courts would be filled with reports about such cases, when it was appreciated that these drugs were the most commonly used by medical men because they were found to be the most reliable and effective hypnotics. Compare this with the illuminating lists prepared and shown in this discussion by Dr. Gillespie. When properly given, the barbituric acid group were the most valuable of all sedatives, and by giving them, even for long periods when necessary, many men retained their mental activity very late in life.

Sir William Willcox was a friend of his (the speaker's), and as Sir William spoke so emphatically against their use it was necessary that those with a long and very different experience should be equally outspoken.

With regard to habit-formation, all he could say was that he had known endless persons take drugs of the barbitone group, but had never seen one of them become a drug addict, and each person could give it up if advised to do so by his medical attendant. Veronal addicts that he had known were persons who would take any drug, and the addiction had usually begun with morphia.

He had been sorry to hear Sir William Willcox say that the barbituric acid group of drugs might be included in the list for restriction. This might make many patients afraid of taking them when prescribed by a medical man. Suicides usually came in waves in respect to the means employed; when a case of death from taking veronal was reported in the newspapers, other cases of the same kind followed. That was so in the aspirin group, ten or twelve of these having been reported within twelve months. It showed the danger of publishing those cases, as it taught people how they could kill themselves. Very few drugs in the pharmacopœia would not kill if taken in an overdose or used improperly. He fully agreed with those who said that small doses of these drugs given regularly was much better than larger ones spaced at greater intervals.

His work was largely to try to prevent people from having a nervous breakdown or becoming insane, and to keep them well once they had recovered.